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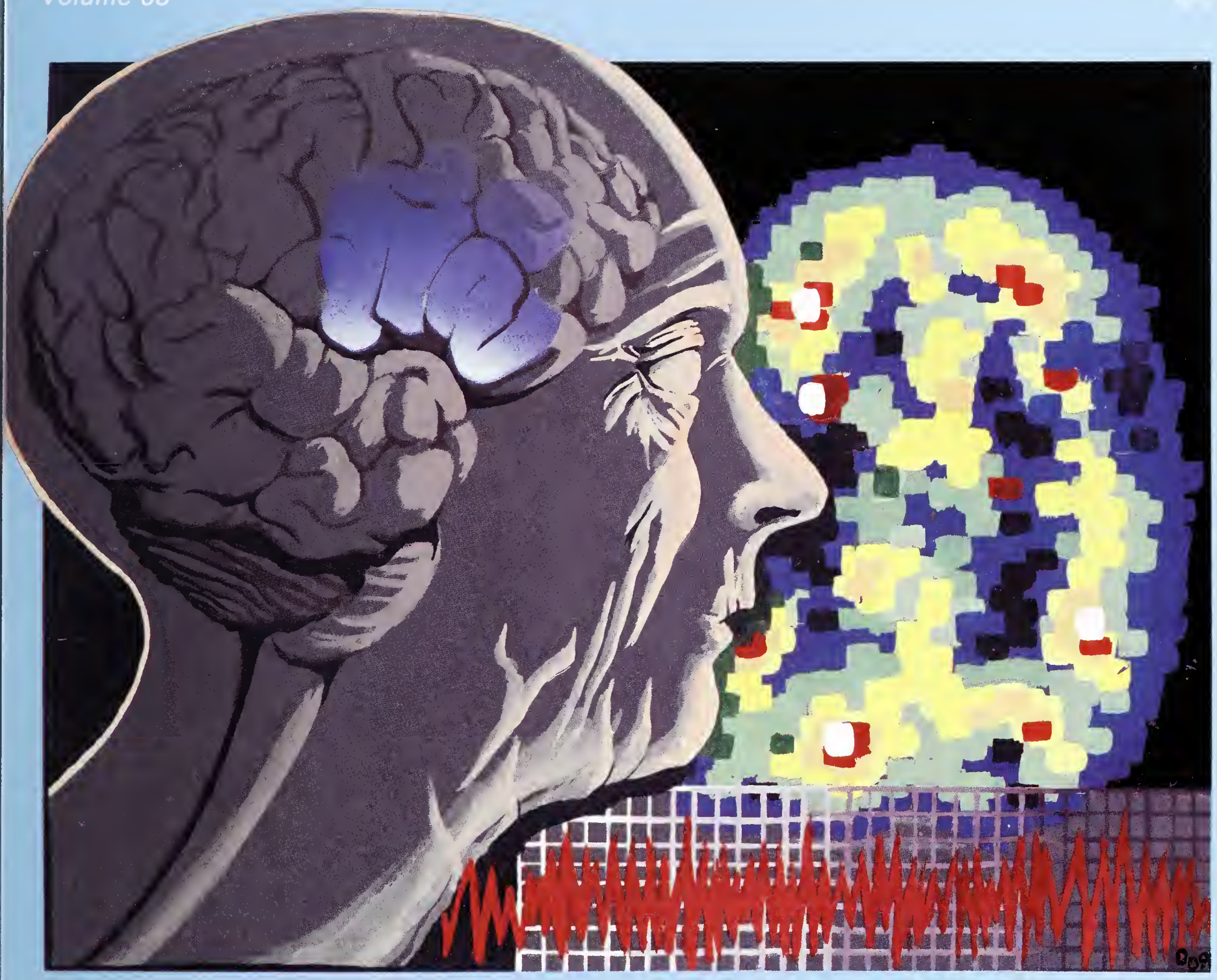
# MEDICAL JOURNAL

Volume 68



• Facial Reanimation: The Surgical Management of Facial Palsy • The Role of Oncogenes in Determining Primary Radioresistance • Functional Neuroimaging • Bone Metastasis: Radiotherapy for Effective Palliation of Pain • The Principles of Osteochondral Allografts • Euthanasia: On Intending Death • Impressions • Quick Diagnosis • News and Views • Book Reviews

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# Editorial

*Mark Bradley Noss*
*Shanthi Vasudevan*

The first issue of this year's University of Toronto Medical Journal was well received. The articles were of outstanding quality and we welcome articles for future issues in the fields of Basic Science, Clinical Medicine, Community Health or any other field of common interest to medical students, practioners and the general readership .

We would like to express our gratitude to Dr. Marvin Auerbach who has established an award on behalf of his brother, the Late Dr. Berney Auerbach, a former editor of the U of T Medical Journal. We wish to thank him for his generosity and support.

Despite the inclement weather, the benefit concert was a success. We are very grateful to Mrs. Ranganathan, Dept. of Music, Queen's University, Dr. Kallury Rao, Dept. of Chemistry, University of Toronto and Meera Krishnan for their splendid performance. We would also like to thank all those people who donated their time and money for such a worthy cause.

This issue features articles which will be of interest to our diverse readership. The feature article on functional neuroimaging describes advances in SPECT imaging. This new imaging technique demonstrates tremendous potential in the diagnosis of dementia. This issue also includes articles on the role of oncogenes in the radioresistence of primary tumours, the effects of radiotherapy in relieving pain caused by bone metastasis, the principles of osteochondral allografts and facial reanimation. Also published in this issue is the runner-up essay of the first annual Biomedical Ethics Essay Competition. This article addresses the issue of euthanasia. We are proud to include coverage of the 1990 Gairdner Awards. We feel that this adds a new dimension to the Journal. The Quick Diagnosis features rapid interpretation of arterial blood gases and pulmonary function tests.

Again, we wish to remind our readers that several prizes are available for the best articles published. Please see inside for details.

Finally, we would appreciate feedback from our readers. Please send us your comments, thoughts and/or impressions for our **'Letters to the Editor'** section.


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Dear Reader,

Thank you for responding to our letter in the first issue. New information has come to light to help us understand that we did not qualify for a Federal Sales Tax Exemption. Therefore, we need to raise approximately $8,000.00 to pay outstanding taxes. We apologize for any misunderstanding generated by our first letter, but the problem remains just as crucial for the Journal.

In order for the Medical Journal to survive, your monetary assistance is urgently requested. Any financial assistance on your part would be greatly appreciated. Thanking you in advance, we remain

Respectfully yours

Shanthi Vasudevan and Mark Bradley Noss
Editors-in-Chief

# Facial Reanimation: The Surgical Management of Facial Palsy

*ARIEL A. WAITZMAN, 9T2 and RONALD M. ZUKER, M.D., F.R.C.S.(C)., F.A.C.S.**

**Associate Professor, Department of Surgery, University of Toronto; Head, Division of Plastic Surgery, The Hospital for Sick Children, Toronto, Canada.*

ABSTRACT

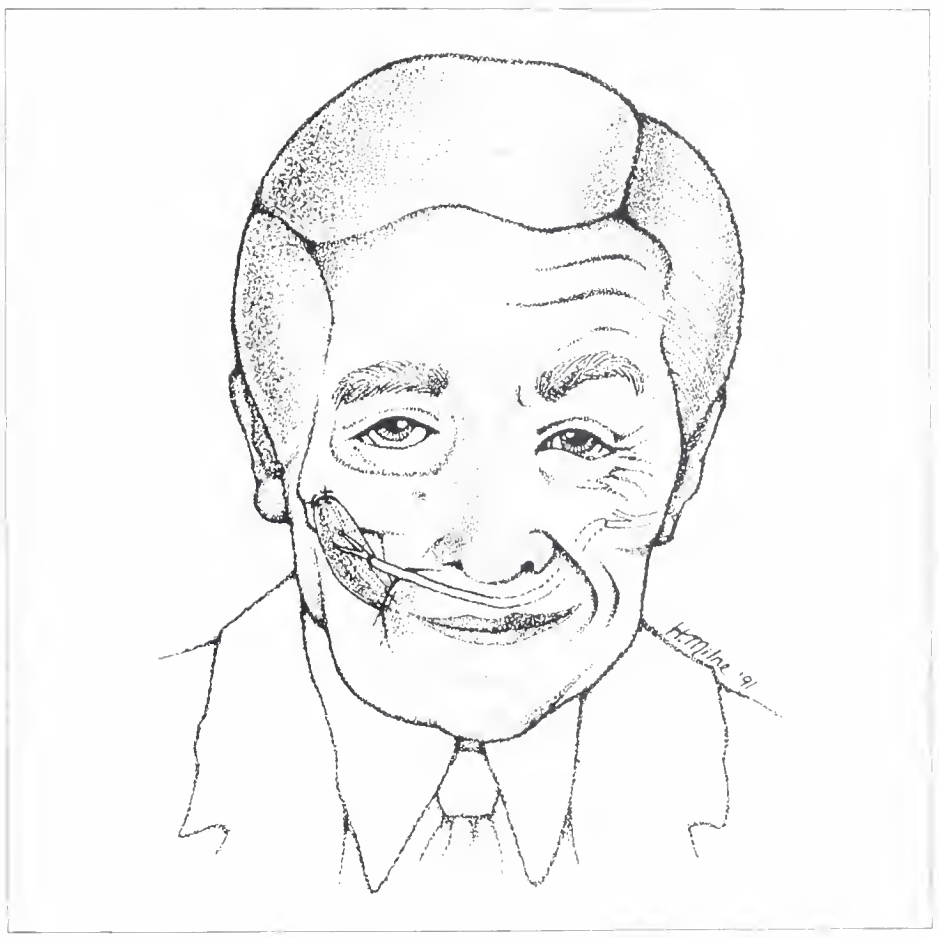
**Patients with facial paralysis may present with a variety of aesthetic and functional problems. In this review the etiology and diagnosis of facial nerve palsy, and indications for various treatment methods along with an outline of each surgical procedure are discussed. Emphasis is put upon the newer microneurovascular techniques. The use of free vascularized muscle transplants allows for facial symmetry at rest, a balanced smile, and spontaneous facial expression with emotion.**

ABSTRAIT

**Des patients avec une paralysie faciale peuvent se presenter avec une variete de problemes esthetiques et fonctionnels. Dans cet article, l'etiologie et la diagnose d'une paralysie au nerf facial sont discutees. Les indications pour differentes methodes de traitement sont decrites avec un apercu de chaque procedure chirurgicale. L'emphase est mise sur les nouvelles techniques microneurovasculaires. L'utilisation de transferts de muscles libres et vascularises permet une symetrie du visage au repos, un sourire equilibre ainsi qu'une expression faciale spontanee avec emotion.**

## *INTRODUCTION*

Paralysis of the facial nerve (CN VII) presents a special challenge to reconstructive surgeons. Affected individuals suffer from both aesthetic and functional impairments. Often these deficits lead to problems in social interaction, and the development of concurrent psychological difficulties[1].



## *ANATOMY OF THE FACIAL NERVE*

The facial nerve consists of 3 main components: motor supply to the muscles of facial expression, visceral efferents (parasympathetic) to the salivary glands (except the parotid), and visceral afferents (taste) from the anterior two thirds of the tongue[2]. The motor nucleus lies in the lower pons. The axons originating in this nucleus encircle the abducens nucleus and then exit the brain stem at the lateral aspect of the cerebellopontine angle. Visceral afferent and efferent fibers terminate and arise in the nucleus/tractus solitarius and superior salivary nucleus respectively, and accompany the facial nerve as the nervus intermedius. Running adjacent to the vestibulocochlear nerve, the facial nerve enters the internal auditory meatus. Some of the parasympathetic fibers enter the greater petrosal nerve to eventually innervate the lacrimal gland. The facial nerve then passes through the facial canal, branching to form the nerve to stapedius and the chorda tympani (salivation and taste). The facial nerve exits the skull via the stylomastoid foramen and divides into its terminal branches between the superficial and deep components of the parotid gland[3,4].

There are five main terminal branches of the facial nerve (temporal, zygomatic, buccal, mandibular, and cervical). When examined by topical organization, the facial nerve has three main areas of innervation, each represented by a separate nerve fascicle. Fascicle 1 (perioral) innervates the orbicularis oris, fascicle 2 the orbicularis oculi, and fascicle 3 (mimetic) innervates all other muscles of facial expression[5]. This, however, is an oversimplification of the facial nerve organization. The facial nerve has been found to communicate by more than 32 branches with the 5th, 8th, 9th, and 10th cranial nerves, the otic ganglion, and sympathetic fibers[6].

## *FACIAL PALSY*

Facial nerve paralysis leads to reduced or absent voluntary and spontaneous facial movements, a lack of resting tone of the facial muscles, and functional difficulties. These deficits may be accentuated by a relative hyperactivity of the contralateral normal

Functional and aesthetic reconstruction is usually [illegible] three regions; the forehead, the eye, and the [illegible] nal problems resulting from lack of tone about the [illegible] neal exposure, leading to irritation, injury and excessive tearing. Corneal ulceration and scarring may occur, eventually leading to blindness. Oral functional difficulties include drooling and pocketing of food in the buccal cavity[7,8]. Both the aesthetic and functional impairments may vary tremendously in severity and location.

**Table 1: Etiologies of Facial Paralysis**

| | |
|---|---|
| Congenital | Idiopathic (isolated), Moebius syndrome, dystrophia myotonica, Bell's Melkersson's syndrome, hemifacial microsomia. |
| Traumatic | Basal skull fractures, middle ear injury, facial injury, altitude paralysis, forceps delivery, molding trauma at birth. |
| Infectious | Otitis externa, otitis media, mumps, mastoiditis, chickenpox, herpes zoster oticus, encephalitis, poliomyelitis, leprosy, mononucleosis, influenza, malaria, syphilis, sarcoidosis, Coxsackie virus, Bell's palsy. |
| Metabolic | Diabetes mellitus, hyperthyroidism. |
| Neurologic | Stroke, multiple sclerosis, myasthenia gravis, Guillian-Barré syndrome. |
| Neoplastic | Cholesteatoma, 7th nerve tumor, glomus jugulare, leukemia, meningioma, teratoma, hemangioblastoma, carcinoma, hemanigioma of eardrum, hydradenoma of external canal, osteopetrosis, schwannoma, sarcoma. |
| Toxic | Thalidomide, tetanus, diphtheria. |
| Iatrogenic | Parotid surgery, mastoid surgery, post tonsillectomy and adenoidectomy, mandibular block anaesthesia, intracranial procedures. |

The ideal reconstruction of facial paralysis would achieve facial symmetry at rest, separate and selective function of the various muscle groups, spontaneous and appropriate mimetic (facial expression) function, no loss of important motor functions (ie. from donor sites), and rapid restoration of tone and motion[9]. Unfortunately no single procedure can alleviate all the components of a facial palsy, and all present treatment strategies achieve less than optimal results[10].

## *ETIOLOGY OF FACIAL NERVE PALSY*

As presented in Table 1, there are many etiological mechanisms that may cause facial paralysis[4,11,12]. The most common form of facial paralysis is a Bell's palsy, with an incidence of 23/100,000 per year[13]. Bell's palsy is most likely due to a viral-inflammatory-immune disorder, characterized by a viral prodrome causing changes in taste, pain around the ear, and numbness in the face and tongue. Sixty percent of patients experience an upper respiratory tract infection or gastroenteritis one to three weeks before the palsy occurs. A primary disorder of the sensory fibers causing edema and compression of the motor axons in the facial canal is thought to be responsible for the paralysis. Seventy to 85% of patients with this condition fully recover within about 4-8 weeks, while approximately 15% go on to severe degeneration[11]. Other lesions of the facial nerve, which usually heal well with minimal permanent deficit, are neurapraxic injuries (nerve compression with temporary interruption of axoplasmic flow), and a cleanly divided nerve which is repaired directly. Of those patients requiring reconstruction for facial palsy at the Hospital for Sick Children and Toronto General Hospital, the most common etiology was congenital, followed by post traumatic and neoplastic. Bell's palsy and other post infectious lesions were in the minority[7]. The incidence of congenital facial palsy is thought to be 0.9/1000[13].

## *DIAGNOSIS*

The diagnosis of facial palsy is relatively simple. However, the resultant facial paralysis is only a symptom, and it is imperative that the underlying disease process be identified. A proper history and physical examination are essential. The site of the lesion can often be determined by testing the end organs of branches of the facial nerve. Alterations in taste, hearing, and salivation are useful clues, and may be elicited using special tests during the physical exam. If necessary, the lesion can be precisely located using electrodiagnostic tests including electromyography and nerve conduction studies, tomography, CT scanning, or MRI[7,14]. A summary of the different anatomic sites of a lesion, the signs produced, and the differential diagnosis is presented in Table 2[4,11]. Special procedures such as CT or MRI are often warranted to rule out a tumor as the cause of a facial palsy.

## *TREATMENT*

Numerous approaches have been developed for the treatment of facial paralysis. Techniques for reconstruction may be divided into static and dynamic procedures. The static procedures may achieve symmetry at rest and improve functional deficits. They do not, however, promote facial movement, and therefore are generally used in cases where a rapid functional improvement is needed, or the rehabilitative potential is low[7]. Methods such as blepharoplasties, tarsorrhaphies, cartilage grafting, and fascia lata slings may be particularly useful for treating a paralytic lower lid ectropion[8]. For example, in patients with a paralyzed orbicularis oculi muscle, the continual pull of gravity draws the atonic lower lid into a progressively sagging position. The patient becomes unable to fully close the eye, and the altered tear flow mechanics cause accumulation of tears in the middle of the lower lid, which then roll onto the cheek[8]. Static procedures may also be employed about the mouth. Slings made of synthetic materials like marlex, teflon or dacron, and autogenous materials like fascia lata or dermis, may be used to suspend the corner of the commissure of the mouth. Rhytidectomies (facelift procedures) also have some applications in this respect[6,7].

## Table 2: Diagnosis of Facial Paralysis

| Level of Lesion | Investigations | Signs | Diagnosis |
|---|---|---|---|
| Supranuclear | CNS exam, CT, MRI | Good tone, intact upper face, spontaneous smiling, neurological deficits | Trauma, CVA |
| Nuclear (Pons) | CNS exam, CT, MRI | 6th & 7th cranial nerves involved, corticospinal tract signs | Vascular or neoplastic poliomyelitis, multiple sclerosis, encephalitis |
| Cerebello-pontine angle | CNS exam, CT, MRI | 5th, 8th, 9th, 10th & 11th cranial nerve involvement, altered taste, lacrimation or salivation. | Meningioma, neurinoma cholesteatoma, fracture, arachnoid cyst |
| Geniculate ganglion | Tear test, CT, MRI | Facial paralysis, hyperacusis, altered taste, lacrimation, or salivation | Herpes zoster oticus, eracture, cholesteatoma, Bell's Palsy, AVM, neurinoma Meningioma |
| Tympano-mastoid | Stapedial reelex, taste, salivation | Facial paralysis, altered taste or salivation, intact lacrimation | Bell's palsy, fracture, cholesteatoma, infection |
| Extracranial | Facial movement | Facial paralysis, intact taste and salivation, jaw deviation to normal side | Trauma, tumor, parotid carcinoma, pharyngeal carcinoma |

Dynamic procedures always supersede other treatment options if applicable. These techniques range in complexity from simple partially dynamic procedures to assist eye closure, such as surgical implantation of metal springs, gold weights, or magnets into the eye lids, to intricate microsurgical approaches[8,16-18].

Early direct repair of an interrupted facial nerve is the treatment of choice. Distortion of the neuromuscular architecture and attrition of mimetic muscles are minimized, resulting in an optimal outcome[6,7,9]. If a gap exists between the proximal and distal ends of the nerve, or if a tensionless repair is not possible, an interpositional nerve graft should be performed. The first successful facial nerve graft was reported by Bunnell in 1927[19]. However, few were attempted until 1950, when trauma victims from World War II and patients undergoing radical resections for parotid gland tumors sparked interest in facial nerve grafting[20]. The sural nerve is usually used as the donor graft. It is a long nerve with few branches along the major part of its course. Exposure and removal of the nerve from the donor site is relatively simple, and the patient experiences minimal functional loss[21]. Both intra and extra-cranial grafting are possible, therefore a wide variety of lesions may be bypassed[22]. The use of the proximal segment for axonal input, and the peripheral segment of the facial nerve for directing the regenerating axons, usually provides a good result. Typically some deficits will be present after healing. General weakness, tightness, and slight spasticity, along with decreased coordination, synkinesis, discrepancies in spontaneous expression, and some regional atrophy are all possible complications. These deficiencies may be due to reduction or misdirection of axon growth, effects of scar tissue about the neural supportive structures, muscular atrophy, and the loss of a certain percentage of central nuclei[6].

If the proximal stump of the facial nerve is not available, a cross-facial nerve graft is indicated. This technique was first demonstrated by Smith with limited success[10]. Anderl[18] modified this approach using multiple grafts and a two stage procedure, with better results. In the first stage, sural nerve grafts are anastomosed to branches of the facial nerve on the normal side. The grafts are then tunnelled across the face using small incisions, and the distal ends are banked on the paralysed side of the face. Four to six months later, a distal anastomoses is performed to attach the grafts to the peripheral branches of the paralyzed facial nerve[18]. The peripheral distribution of the donor facial nerve is important. If properly selected, several small branches of the donor facial nerve can be sacrificed without disturbing the function of the normal side. This is due to the abundant nerve supply to the facial muscles and the extensive interfascicular ramifications of the facial nerve, which provides for coverage of the sacrificed axons by the remaining branches[18]. The facial nerve has excellent regeneration potential, although the results of a cross-facial nerve graft never achieve the quality of an ipsilateral repair[18,23,24]. It has been the experience of the senior author and others[10], that although it may provide some tone about the eye, a cross-facial nerve graft alone does not provide enough innervation power to produce a satisfactory smile. Therefore, to reconstruct a smile, the cross-facial nerve graft is followed by a free muscle transplant. Other authors have used cross-facial nerve grafts as an isolated procedure, and are satisfied with the results[18].

*Figure 1. Free Segmental gracilis transfer with vascular pedicle aligned on patient's face.*

Nerve transfer procedures have also been described and proven useful for facial palsies when the facial musculature is adequate. Although several cranial nerves have been utilized, the most successful to date is the hypoglossal to facial (CN XII to CN VII) transfer, as popularized by Baker and Conley[25]. Resting tone and voluntary movement are often adequate, but there can be no spontaneous facial expression. Movement of the paralyzed side is usually present 4-6 months after the procedure, but the patient must be retrained to push their tongue against their teeth when facial movement is desired[6]. The patient's smile often resembles a grimace, due to the mass movement or synkinesis when the hypoglossal nerve simultaneously stimulates all the muscles[7]. The hemiparesis of the tongue may also be problematical. Deficits in speech and eating may occur, along with atrophy of the denervated half tongue, which is severe in 25% of the cases[6,26].

If a patient presents within 6-12 months of the onset of facial paralysis, then a nerve repair or graft is the treatment of choice. However, for a long standing paralysis, with absent, or atrophied and fibrosed muscles, other reconstructive strategies are required[27]. In this situation, muscle transfers, which can provide functional and aesthetic improvement quickly, and are not as difficult to perform surgically as many other procedures, are indicated. Muscle transfers using masseter, temporalis, platysma, frontalis, and sternocleidomastoid have been performed. Masseter and temporalis transfers have been the most successful and popular of these procedures[6,25]. The insertion of the muscle to be transferred is dissected to a variable extent, and reattached by sutures to the area requiring reanimation. Usually the masseter is used for smile reconstruction, with a new insertion created in the upper and lower lips and oral commissure. The temporalis may be used for either perioral or periocular reconstruction. Although these procedures provide symmetry at rest and some voluntary movement, there are several drawbacks. The origin of the transferred muscle is fixed, therefore the muscle cannot be placed exactly where needed. The patient must be re-educated to use the trigeminally innervated muscle for facial gesture by clenching teeth and moving their mandible. As with nerve transfer procedures, spontaneous facial expression is impossible, and donor site morbidity may be a problem (eg. chewing difficulties)[25]. The voluntary movement gained is often inadequate, resulting in an asymmetrical smile.

## *FREE MUSCLE TRANSPLANTS*

The concept of free muscle grafting for the treatment of facial paralysis was introduced by Thompson in 1971[28]. Free composite grafts, which have been selectively denervated two weeks prior, are used. The grafts are sutured into place on the paralyzed side of the face. Reinnervation occurs by the process of neurotization (growth of new axons into the muscle) through intact underlying muscle. The lack of vascular reanastomosis requires the graft size to be very small. This greatly limits the value of this procedure, since the contractile force necessary for facial movement cannot be obtained[28,29].

Advances in microneurovascular surgical techniques have allowed the development of free vascularized muscle transplants[30]. These microsurgical procedures are presently considered state of the art for many difficult reconstructive challenges. Free vascularized muscle transplants were first used to replace forearm flexors lost either to trauma or Volkmann's ischemic contracture[30]. As techniques developed, applications for footdrop, loss of forearm and knee extensors, loss of elbow flexors, and facial paralysis were discovered[24,28,30-35]. The proper choice of a donor muscle is imperative. A muscle with the correct amount of viable bulk for the force of contraction needed, and the proper fiber length for the range of excursion required, is selected. The resting tone of the transplanted muscle and quality of neurovascular anastomoses are important for functional recovery. A muscle restored to normal resting length, will have a normal resting tone at its new anatomical site[12]. A meticulous nerve repair, is carried out as close to the transplanted muscle as possible, to minimize the time needed for muscle reinnervation to occur. Experimental and clinical evidence demonstrate that three hours of muscle ischemia is safe, and that up to four hours of ischemia does not affect the final outcome of a muscle transplant[36]. This allows for a careful and well planned repositioning and revascularization of the donor muscle. If all goes well, reinnervation, documented by EMG studies, may be apparent by as early as 6 weeks[12].

The preferred muscle for facial reanimation at the Hospital for Sick Children and Toronto General Hospital is currently the gracilis[37]. Other muscles, such as serratus anterior, latissimus dorsi, and pectoralis minor are also described as being useful. The extensor digitorum brevis, based on the dorsalis pedis vessels, has been used. However the contractile force of this muscle is generally inadequate, and the results are poor[10,27]. The gracilis has an ideal neurovascular pedicle (6-7 cm), based on a central artery, paired venae comitantes, and the motor nerve to gracilis (a branch of the obturator nerve). The donor deficit is unnoticeable, and the scar at the donor site is well hidden. The muscle itself can be tailored to the correct size and shape needed[38].

Congenital facial palsies may be simple or complex. The complex forms are part of syndromes, such as hemifacial microsomia or Moebius syndrome (severe bilateral facial paralysis). Simple or isolated cases generally have minimal functional problems, with corneal protection and oral competence usually being ad-

equate[23]. The upper lip and oral commissure are affected most, resulting in asymmetry at rest, a poor smile, and increased commissure and cheek droop over time. Smile reconstruction, therefore, becomes the focus of attention for cases of congenital facial paralysis[23].

In a normal subject, all muscles affecting smile, except the buccinator and risorius, originate in bone and insert into the orbicularis oris. Some of these muscles penetrate the orbicularis and end in skin around the mouth or vermilion (red lip). The contraction of these muscles throws skin perpendicular to the muscle fibers into folds, creating the skin wrinkle lines. The large variation in smiles is a consequence of the direction and strength of the various muscles, and the placement and extent of the skin folds[39]. A single transplanted muscle cannot replicate the fine coordinated intricate movements of the facial musculature. However, a vascularized muscle transplant can provide good resting tone, a symmetrical smile, and importantly, spontaneous activity with emotion[23]. Children with congenital facial paralysis should complete their reconstruction around age five, before they enter the first grade. After this age, the effects of childhood teasing, social embarrassment, and reduced social interaction often appear, with sometimes dire consequences. The.muscle transplant grows with the patient, therefore further procedures are not usually needed[23].

## *OPERATIVE PROCEDURE*

Prior to surgical intervention the oral configuration is studied. The normal side is measured for midline deviation at rest, and when smiling actively. This assists in determining the location and direction of desired movements on the paralyzed side, and therefore the correct placement of the muscle. The facial vessels, later to be anastomosed to the transplant, are assessed by palpation or Doppler probe[23,38].

The first stage of the procedure is cross-facial nerve grafting. At operation, a preauricular incision is performed on the normal side. Branches of the facial nerve are identified as they exit the anterior portion of the parotid fascia, and mapped using a nerve stimulator. Three to five fascicles, whose actions are covered by remaining branches, are selected for division[38]. A sural nerve graft is then removed from the calf. The graft is reversed and tunnelled across the face using small nasal vestibular incisions. The distal nerve graft end is placed high on the maxilla or zygoma of the paralyzed side, tagged and then banked. A fascicular repair using 11-0 nylon sutures is performed between the proximal end of the nerve graft and the selected facial nerve branches. The regeneration of axons across the graft can be monitored using Tinel's sign[18,38,40,41].

Nine to twelve months later, the second operative stage is carried out. The gracilis is exposed using a longitudinal incision in the medial thigh. The motor nerve and vessels supplying the gracilis are then identified. The nerve is meticulously dissected into 2-4 fascicles. Each fascicle is tested using a nerve stimulator, and the gracilis is then divided into territories based on individual fascicular nerve supply[32,40]. These muscle fiber territories are relatively discrete, allowing for separation of muscular segments. To reconstruct the oral region, the anterior one third of the gracilis

*Figure 2a. Right sided unilateral facial palsy, preoperative view.*

*Figure 2b. Right sided unilateral facial palsy, postoperative view.*

is then removed, along with its neurovascular pedicle. The remaining muscle is left in situ, being well perfused by the one or two neurovascular pedicles[38].

With the gracilis segment is removed, a second team can prepare the facial area. A preauricular incision with submandibular extension is performed of the paralyzed side. The previously banked nerve graft is identified and evaluated histologically, with the best fascicles being selected. A subcutaneous pocket is created for the muscle transplant. The gracilis segment is then custom tailored to the required size and shape, and placed within the dissected pocket (Fig.1). Sutures are placed carefully, with intra-operative testing, to attempt to replicate the activity of the normal side[38]. The most inferior suture is placed in the lateral margin of the lower lip, creating a commissural fold. The middle suture is placed in the commissure. The most superior suture is placed in the upper lip, creating a nasolabial fold. The origin of the transfer is then anchored to the periosteum of the zygomatic arch or body of the zygoma. This orientation corresponds to the normal position of the zygomaticus major, a muscle important in smiling[38].

The vascular anastomoses are then carried out, securing the gracilis vessels to the facial (or superficial temporal) vessels, with 10-0 nylon sutures. The nerve repair, between the cross-facial nerve graft and gracilis nerve, is completed with 11-0 nylon sutures. Once all anastomoses are complete, and incisions closed, a prefabricated hook is placed in the patient's mouth. This appliance relieves tension at the insertion, and is removed in 10 days. Reinnervation of the graft is usually evident within six months. At this time an active exercise/biofeedback programme is begun, which increases the strength and excursion of the graft, and improves facial symmetry. The final results of this procedure are generally very pleasing. Symmetry at rest is restored as muscle imbalance is eliminated. Previous problems of excess bulk are avoided by using only a segment of the gracilis. Muscle excursion is typically just under 1 cm, which is quite adequate for producing a balanced smile (Fig.2). The use of the facial nerve as a neural input, assures spontaneity of contraction with emotional expression, an important goal never reached in these patients before free muscle transplants were developed[38,41].

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## *REFERENCES*

1.Zuker RM, Manktelow RT. A smile for the Moebius' syndrome patient. Ann. Plast. Surg. 1989; 22:188-194.
2.Sullivan JA. Surgical techniques on the facial nerve. Arch. Otolaryngol. 1963; 78:434-442.
3.Gilman S, Newman SW. Functional components of the cranial nerves. In Manter and Gatz's essentials of clinical neuroanatomy and neurophysiology. Philadelphia: F.A. Davis Company, 1987: pp 108-110.
4.Lindsay KW, Bone I, Callander R. Facial weakness. In Neurology & neurosurgery illustrated. New York: Churchhill Livingstone, 1986: pp 153-158.
5.Kempe LG. Topical organization of the distal portion of the facial nerve. J. Neurosurg. 1980; 52:671-673.
6.Conley J. Facial rehabilitation: New potentials. Clin. Plast. Surg. 1979; 6:421-431.
7.Wells MD, Manktelow RT. The surgical management of facial palsy Ann. Plast. Surg. (in press)
8.Jelks GW, Smith B, Bosniak S. The evaluation and management of the eye in facial palsy. Clin. Plast. Surg. 1979; 6:397-419.
9.Tucker HM. Restoration of selective facial nerve function by the nerve-muscle pedicle technique. Clin. Plast. Surg. 1979; 6:293-300.
10. O'Brien BM, Franklin JD, Morrison WA. Cross-facial nerve grafts and free muscle transfer for long established facial palsy. Brit. J. Plast. Surg. 1980; 33:202-215.
11. May M. Facial paralysis: Differential diagnosis and indications for surgical therapy. Clin. Plastic Surg. 1979; 6:275-291.
12. McKee NH, Kuzon WM. Functioning free muscle transplantation: Making it work? What is known? Ann. Plast. Surg. 1989; 23:249-254.
13. Hauser WA, Karnes WE, Annis J, Kurland LT. Incidence and prognosis of Bell's palsy in the population of Rochester, Minnesota. Mayo Clin. Proc. 1971; 46:258-264.
14. Collier J. Electrodiagnosis and surgical indications in facial palsy. Arch. Otolaryngol. 1963; 78:421-426.
15. Hill HL, Vasconez LO, Jurkiewicz MJ. Method for obtaining a sural nerve graft. Plast. Reconstr. Surg. 1978; 61:177-179.
16. Morel-Fatio D, Lalardrie JP. Palliative surgical treatment of facial paralysis. The palpebral spring. Plast. Reconstr. Surg. 1964; 33:446-456.
17. Muhlbauer WD, Segeth H, Viessmann A. Restoration of lid function in facial palsy with lid magnets. Chir. Plast. 1973; 1:295-304.
18. Anderl H. Cross-face nerve transplant. Clin. Plast. Surg. 1979; 6:433-449.
19. Bunnell S. Surgical repair of the facial nerve. Arch. Otolaryngol. 1937; 25:235.
20. Millesi H. Nerve suture and grafting to restore the extratemporal facial nerve. Clin. Plast. Surg. 1979; 6:333-341.
21. Baker DC, Conley J. Facial nerve grafting: A thirty year retrospective review. Clin. Plast. Surg. 1979; 6:343-360.
22. Dott NM. Facial nerve reconstruction by graft bypassing the petrous bone. Arch. Otolaryngol. 1963; 78:426-428.
23. Zuker RM. Facial paralysis in Children. Clin.Plast. Surg. 1990; 17:95-99.
24. Manktelow RT. Facial paralysis reconstruction: Functioning muscle transplantation. In Manktelow RT (Ed), Microvascular reconstruction: Anatomy, applications and surgical techniques. Berlin: Springer-Verlag, 1986: pp 128-164.
25. Baker DC, Conley J. Regional muscle transposition for rehabilitation of the paralyzed face. Clin. Plast. Surg. 1979; 6:317-331.
26. Stennert E. Hypoglossal facial anastomosis: Its significance for modern facial surgery. Clin. Plast. Surg. 1979; 6:471-486.
27. Tulhurst DE. Free revascularized muscle grafts in facial palsy. Plast. Reconstr. Surg. 1982; 69:760-769.
28. Thompson N. Autogenous free grafts of skeletal muscle. Plast. Reconstr. Surg. 1971; 48:11-27.
29. Harii K. Microneurovascular free muscle transplantation for reanimation of facial paralysis. Clin. Plast. Surg. 1979; 6:361-375.
30. Manktelow RT, McKee NH. Free muscle transplantation to provide active finger flexion. J. Hand. Surg. 1978; 3:416-426.
31. Manktelow RT, Zuker RM, McKee NH. Functioning free muscle transplantation. J. Hand. Surg. 1984; 9:32-39.
32. Manktelow RT, Zuker RM, Young SC, Fish J. Neurovascular and muscle fiber anatomy of the gracilis muscle: Applications to facial reanimation. In Frey M, Freilinger G (Eds), Proceedings of the 2nd Vienna muscle symposium. Vienna: Facultas-Verlag, 1985: pp 232-234.
33. Manktelow RT, Zuker RM. Functioning muscle transplantation to the extremities. In Frey M, Freilinger G (Eds), Proceedings of the 2nd Vienna muscle symposium. Vienna: Facultas-Verlag, 1985: pp 283-294.
34. Manktelow RT. Functioning muscle transplantation to the arm. In Terzis J (Ed), Microreconstruction of nerve injuries. Toronto: W.B. Saunders, 1987: pp 267-281.
35. Manktelow RT. Free muscle transplantation for facial paralysis. Clin. Plast. Surg. 1984; 11:215.
36. Kuzon WM, Pynn BR, Fish JS, et al. The effect of intraoperative ischemia on the recovery of contractile function following free muscle transfer. J. Hand Surg. 1988; 13:263-273.
37. Manktelow RT. Microvascular muscle transfer for the extremity and for facial paralysis. In Jackson IT, Sommerlad BC (Eds), Recent advances in plastic surgery 3. Edinburgh: Churchill Livingstone, 1985: pp 123-136.
38. Zuker RM. Microvascular management of facial palsy. Curr. Ther. Plast. Reconstr. Surg. 1989; 157-162.
39. Rubin LR. The anatomy of a smile: Its importance in the treatment of facial paralysis. Plast.Reconstr. Surg. 1974; 53:384-387.
40. Manktelow RT, Zuker RM. Muscle transplantation by fascicular territory. Plast. Reconstr. Surg. 1984; 73:751-755.
41. O'Brien BM, Pederson WC, Khazanchi RK, Morrison WA, MacLeod AM, Kumar V. Results of management of facial palsy with microvascular free-muscle transfer. Plast. Reconstr. Surg. 1990; 86:12-22.

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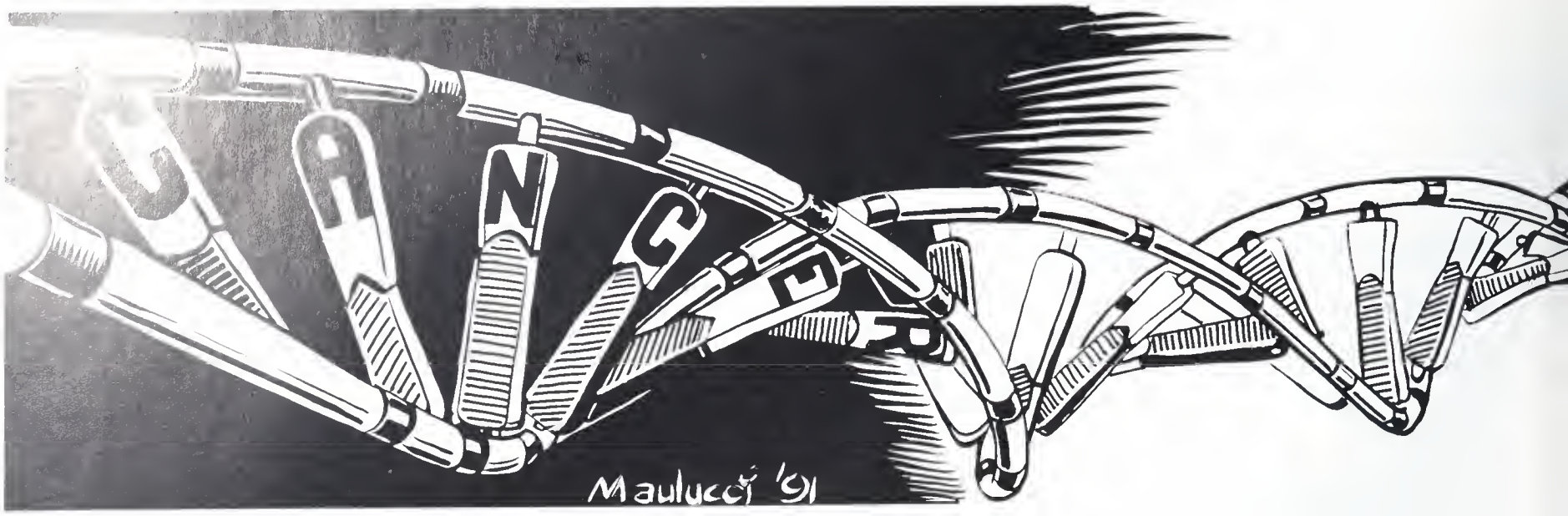


# The Role of Oncogenes In Determining Primary Tumour Radioresistance and Secondary Metastatic Spread

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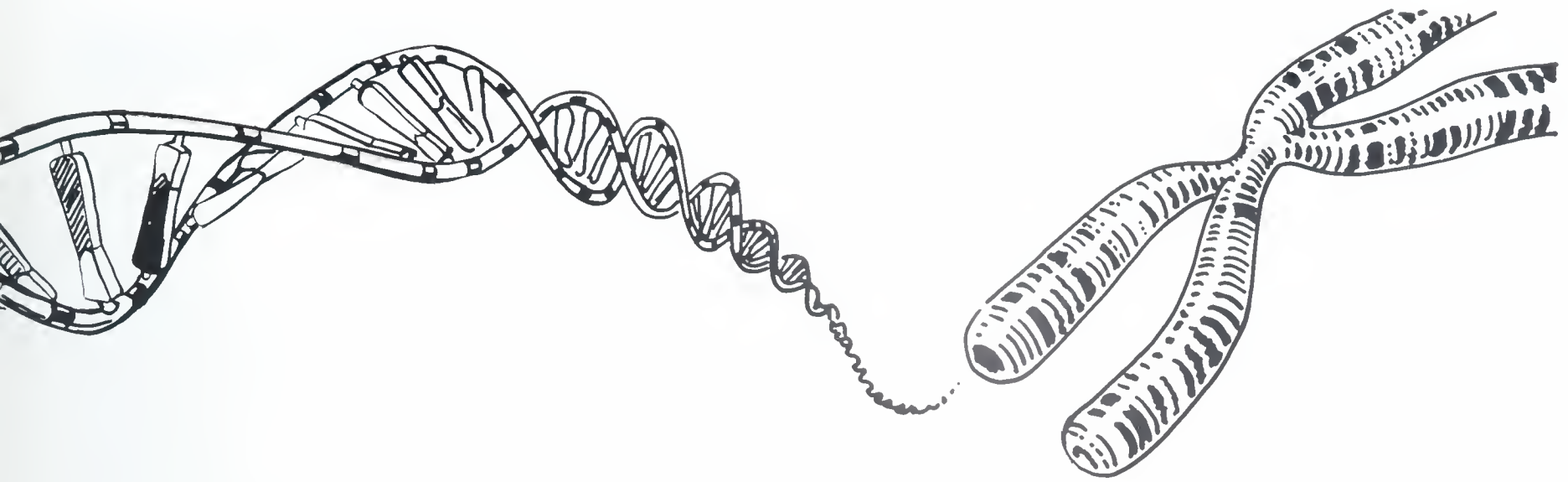
## ABSTRACT

**Cancer therapies may be limited in their effectiveness by the appearance of resistant or aggressive tumour cell variants within a given patient's tumour. Recent transfection studies implicate increased or activated oncoprotein expression in aggressive transformed phenotypes, specifically radioresistant and metastatic tumour cell variants. Such studies provide evidence for the involvement of the cytoplasmic *ras* and cooperating nuclear oncoproteins in this regard. We review recent investigations by our own laboratory and others regarding NIH 3T3 and primary rat embryo fibroblast transfectant models in delineating these aggressive phenotypes. *H-ras* transformants have been found to be variably radioresistant, tumorigenic and highly metastatic (both experimentally and spontaneously) in comparison to untransfected fibroblasts when assayed in strains of immune-deprived mice (ie. nude, NIH III and SCID). Co-transfection of *c-myc* or mutant *p53* can result in a further increase in radioresistance and tumorigenicity. In general, acquisition of radioresistance is associated with greater metastatic ability for a given transfectant. It is proposed that expression of phenotypes associated with oncogenic expression can be modulated and complicated by type of transfection procedure, site of oncogene insertion and micro-environmental factors which can change relative expression within a solid tumour volume.**

## ABSTRAIT

**Malgré qu' en tout premier lieu les séquences oncogènes ont été impliquées dans les processus cancérigènes, les études récentes en transfection démontrent une expression active ou augmentée des oncoproteines dans les phénotypes transformés et agressifs, spécifiquement chez les cellules variantes de certaines tumeurs qui ont (les cellules) des qualités métastatiques et radiorésistantes. Nous avons caractérisé une série de transfectants primaires venant de fibroblastes d'embryon de rats suivant l'introduction de l'oncogène H-ras avec un gène marqueur néo-sélectif, seul ou en combinaison avec les oncogènes c-myc nucléaire, E1a et p53 mutant. Les transformants positifs pour le gène H-ras furent trouvé comme étant radiorésistants, tumorigènes et trés métastatiques (expérimentalement et spontanément) en comparaison aux fibroblastes non transfectées lorsqu'on en fit l'essai dans 3 souches de souries (nues, NIH III et SCID) avec des déficiences immunologiques. La transfection combinée avec c-myc ou p53 mutant a resulté en une augmentation de la radiorésistance. Il y a eu deux résultats inattendus de notre série: (1) les transfectants contenant H-ras et E1a étaient radiosensibles et non métastatiques et (2) la transfection avec le néo-marqueur seul a augmenté la radiorésistance des fibroblastes. En général, l'acquisition de la radiorésistance était associé avec une plus grande capacité métastatique pour un transfectant donné. Il est suggéré que l'expression des phénotypes associés avec des expressions oncogènes peut être modulée et compliquée par le genre de procédure utilisé pour la transfection, le site de l'insertion de l'oncogène et les facteurs du micro-environnement qui peuvent changer l'expression relative à l'intérieur d'un volume de tumeur solide.**



## *THE CLINICAL PROBLEM*

Clinically, tumours are usually treated with surgery, radiotherapy or chemotherapy either alone or in combination. Patient survival depends on the effective treatment of the primary site of disease involvement before the systemic spread of cancer to secondary sites increases the tumour burden to incurable proportions. Ineffective first line therapy may uncover resistant cell populations in the tumours which decrease the probability for cure. Through alliances between basic cancer biologists and clinical oncologists, the molecular genetic basis for resistant cancer cells is slowly being elucidated. The development of a cancer cell involves a series of events, probably genetic and epigenetic, which must occur and interact to transform normal cells. Such events continue to occur during tumour growth leading to the acquisition of various malignant phenotypes (tumour progression), the most aggressive of which will be the ability for metastasis.

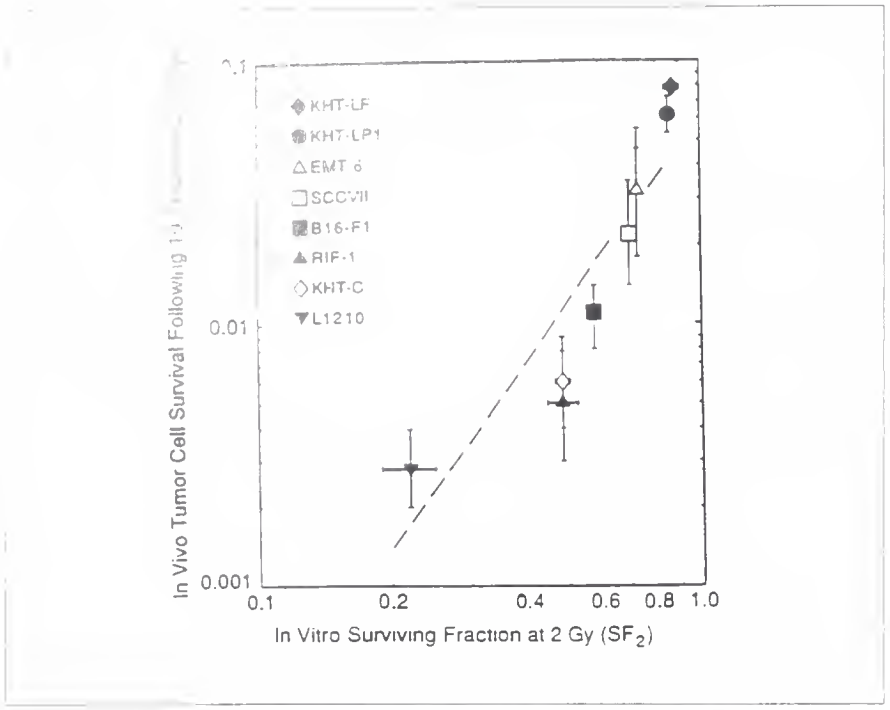
Tumour cell diversification is thought to involve inherent genetic instability, producing alterations in growth regulatory genes. This may then be followed by selection and growth of variants within a tumour cell population through subpopulation interactions and the microenvironment provided by the host (ie. angiogenesis, immunologic mechanisms, mutagenic processes, oxygen and nutrient gradients, and tissue/stromal matrix)[1-3]. Genes attributed to the metastatic phenotype include sequences which encode proteins involved in oncogenesis, tumour suppression, growth requirements, adhesion and matrix-degradation and cell-cell interactions and signalling[4-6].

## *ONCOGENE THEORY*

Oncogenes are a series of genes which have been implicated in the carcinogenic process based on molecular studies of virally-induced animal tumours and transforming ability of DNA derived from spontaneous human cancers[2,7]. Introduction of either viral or human tumour DNA containing oncogenic sequences into a variety of recipient cell lines such as murine NIH 3T3 cells or the more genetically stable and diploid primary rat embryo fibroblasts (REF) is termed "transfection". Transfection has most often been accomplished using calcium phosphate-mediated uptake of DNA, but can also be accomplished through cell membrane-penetrating lipofectin or electroporation techniques. Colonies arising from cells containing the introduced sequences (positive transformants) can be identified either on the basis of morphological changes or selective colony growth in antibiotic media (G418/geneticin) via resistance mediated by a co-transfected dominant resistance marker gene (ie.neomycin).

Transfection studies have shown that some oncogenes can immortalize and morphologically transform cells, as well as confer a tumorigenic phenotype (ie. the membrane/cytoplasmic *ras, src, abl* genes) while others can only immortalize cells (ie. the nuclear *myc, myb*, mutant $p53$[8,9]. Through comparison of sequences between cloned oncogenes from tumour DNA and normal cell DNA, it was found that non-cancerous cells of the body contain the homologues of oncogenes (termed "proto-oncogenes") which are involved in the normal regulation of cellular growth. Should the normal homologues change their protein expression through mutation, chromosome translocation or gene amplification, the cell loses its self-regulatory control and may attain cancerous qualities (ie. the proto-oncogenes become oncogenes). More recently, several tumour and metastasis suppressor genes and their protein products have been cloned (ie. *rb, p53, K-rev-1* and *nm23*); allelic loss or mutation of these genes (resulting in the loss of wild-type or normal protein function) leads to transformation in the presence of other dominant oncogenes[10-12]. For example, it has been shown that transfecting wild-type *p53* or *K-rev-1* sequences will reverse the transforming features of mutant *p53* and *ras* oncogenes respectively[9,13]. Table 1 lists some of the more commonly studied of these genes with the location and hypothesized function of their protein product.

One of the most extensively studied oncogenes in regard to radioresistance and metastasis is the *H-ras* oncogene. This gene encodes the $p21^{ras}$ protein which functions as a sub-cytoplasmic membrane GTPase and it's activity has been altered (remaining GTP-bound in some cases) in tumours through mutations in codons 12, 13 and 61 of RNA encoding the protein[11]. *Ras* has the ability to transform primary rat embryo fibroblasts by itself, but its transformation efficiency is increased when a nuclear oncogene, such as *myc*, adenovirus *E1a* or the mutant form of the tumour suppressor gene, *p53*, is co-transfected, resulting in the "cooperation" of oncogenes[8,9,14]. Evidence for cooperation *in vivo* between



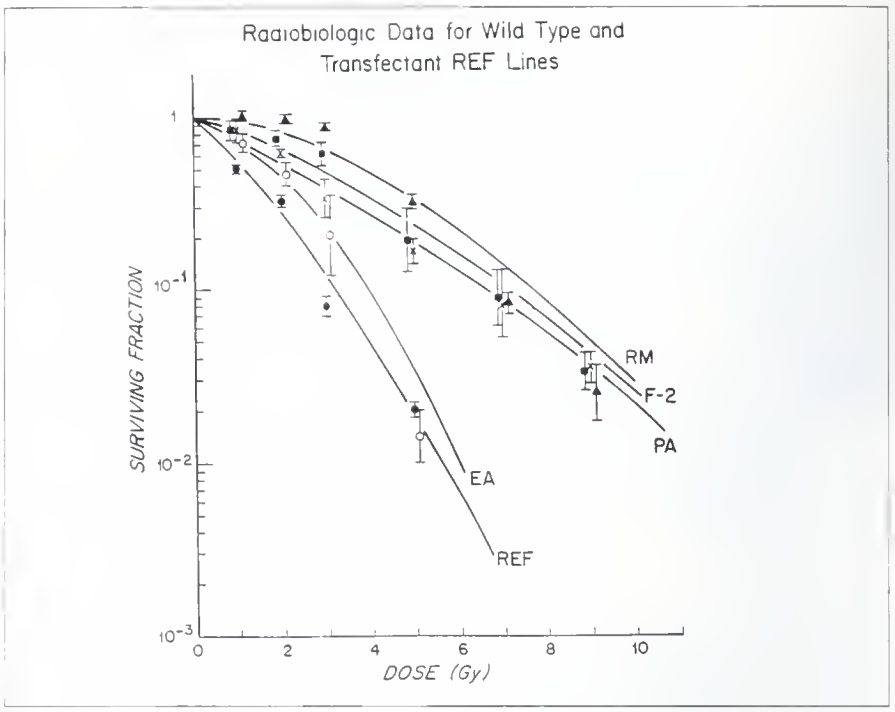




*Figure 1: Evidence for genetic factors in determining radiation sensitivity is supported by strong correlations between* in vitro *radiosensitivity and tumour radioresponse following clinical fractionated radiation treatment (Figure 1a) for 8 experimental murine tumours (correlation coefficient=0.90). In addition, transfection of individual oncogenic sequences can modulate in vitro radiosensitivity of primary rat embryo fibroblasts (Figure 1b). RM denotes* ras *plus* myc *transfectants, F-2 and PA are ras alone or neo marker alone transfectants respectively, EA is* ras *plus E1a transfectants and REF is untransfected fibroblasts. Although not shown, curves for* ras *plus mutant* p53 *or mutant* p53 *alone transfectants are equivalent to RM and F-2 curves respectively.*

*ras* and *myc* came from experiments by Sinn et al.[15] in which transgenic mice were created by introducing either activated *H-ras* or *c-myc* sequences into mouse germ cells and noting the tumour formation in the progeny. Mating the *c-myc* expressing strains with H-ras expressing strains leading to both oncogenes being expressed within a strain resulted in synergistic increases in tumour formation and growth.

There has been enthusiastic investigation into the role of oncogenes, particularly the *ras* and nuclear acting oncogenes, in parallel studies involving the generation of radioresistant and metastatic tumour cell lines. It may be that changes in oncogene expression common to both these phenotypes can account for the clinically aggressive behavior of these cells. Studies which simultaneously compare relative radioresistance and metastatic capability in cell lines of differing oncogene expression may shed light on these issues and a review of these investigations will form the bulk of the ensuing discussion.

## *ONCOGENES AND RADIORESISTANCE*

Radiation therapy is usually given to patients as a series of daily small fractions of high energy X-ray or gamma radiation (1-2.5 Gy) with the hope of sterilizing all tumour clonogenic or stem cells (ie. cancer cells capable of self-renewal) in order to effect tumour cure[16].Traditionally, resistance of cells to radiation damage has been associated with cell kinetic and microenvironmental factors such as: (i) intracellular oxygen and sulfhydryl concentrations (involving indirect free radical damage pathways), (ii) cell cycle phase at the time of irradiation (usually for a given cell line: cells in G2/M are sensitive to irradiation, while cells in late S are resistant), and (iii) the type and quantity of radiation-induced direct and indirect DNA lesions incurred by the cells (ie. double strand breaks)[17,18]. As a result, many radiobiologists and radiation oncologists have centered their efforts on these environmental factors in order to increase cell kill after each dose of radiotherapy (ie. hypoxic cell radiosensitizers, particle beam therapy, accelerated fractionation regimens).

A link between the genetic basis for radioresistance and clinical outcome came from a retrospective analysis of published radiation survival curves by Fertil and Malaise in 1981. They (and subsequently other authors) correlated tumour cell radiosensitivity *in vitro* to the historical clinical radiotherapeutic outcome for each type of tumour[19]. This hypothesis was supported by our own studies involving murine tumour models of varying histopathologic type, which showed experimentally that low dose radiosensitivity *in vitro* correlated with solid tumour radioresponse *in vivo* to fractionated radiation treatment[17,20]. This suggested that in addition to the previous mentioned micro-environmental factors, the genetic ability of a cell to survive clinically relevant radiation doses is an important factor in the clinical outcome of radiotherapy (see Figure 1a) and may one day be used as a predictor of radiotherapy response. Unfortunately, there has been little success in cloning putative ionizing radiation DNA repair genes that could theoretically be used for a molecular predictive assay[21].

A role for oncogene-mediated radioresistance came from initial studies by Sklar[22-23] in which mouse NIH 3T3 cell lines transfected with mutated forms of the *ras* oncogene showed increased survival after radiation compared with similarly untransfected cells or lines transfected with the unmutated ras gene. In addition, McKenna *et al.*[14] using the more genetically stable diploid REF model, has shown that the mutated *H-ras* oncogene can increase radioresistance slightly, but this effect can be increased when a cooperating oncogene such as *c-myc* is co-

**Table 1a: Location and Function of Selected Oncogenes***

| Oncogene | Oncoprotein Location | Oncoprotein Function |
|---|---|---|
| *MYC* | NUCLEAR | REPLICATION, CHROMATIN STRUCTURE |
| *FOS* | NUCLEAR TRANSCRIPTIONAL FACTOR | DNA BINDING; AP-1 COMPLEX |
| *JUN* | NUCLEAR TRANSCRIPTIONAL EACTOR | DNA BINDING, AP-1 COMPLEX |
| *MUTP53* | NUCLEAR PHOSPHOPROTEIN | COMPLEXES WITH P53/HSP70 |
| *SRC* | CYTOPLASMIC TYROSINE KINASE | INCREASES PROTEIN KINASE C? |
| *LCK* | CYTOPLASMIC TYROSINE KINASE | T-CELL ACTIVATION: CD4/CD8 |
| RAF | CYTOPLASMIC SERINE/THREONINE KINASE | SUBSTRATES UNKNOWN |
| *RAS* | CYTOPLASMIC GTPASE | TRANSDUCTION THROUGH PKC |
| *SIS* | GROWTH EACTOR | BETA CHAIN OE PDGF |
| *ERB-B* | MEMBRANE TYROSINE KINASE | MUTANT EGF RECEPTOR |
| *FMS* | MEMBRANE TYROSINE KINASE | MUTANT CSF-1 RECEPTOR |

transfected into the same recipient cell. Supporting data from our laboratory can be seen in Figure 1b. However, studies by Harris *et al.*[24] and Grant *et al.*[25] which tested the correlation between $p21^{ras}$ expression and *in vitro* radiosensitivity/repair endpoints in human and murine lines of varying $p21^{ras}$ expression, failed to substantiate the role of $p21^{ras}$ in mediating radioresistance. Of interest in the latter study however, is the fact that the highest $p21^{ras}$ expressing lines were also the most radioresistant in this series, perhaps arguing for a threshold level of $p21^{ras}$ expression needed to insure a resistant phenotype (a concept to be discussed later).

Other oncogenic sequences associated with the radioresistant phenotype are the *raf* and *myc* oncogenic sequences. Kasid *et al.*[26] found amplification and activation (truncation of 5' end) of the *c-raf* oncogene in transfectants transformed by genomic DNA from a radioresistant, human laryngeal squamous cell carcinoma. Both radioresistance and tumorigenicity were reversed when the authors depleted *c-raf* RNA message with anti-sense RNA constructs. Similarly Chang *et al.*[27] reported activation of *c-raf* and an amplification of the nuclear *c-myc* oncogenes in DNA isolated from radioresistant human fibroblasts sampled from individuals suffering with the cancer-prone Li-Fraumeni syndrome. Such studies prove a correlation, but not causality, for oncogene-mediated radioresistance. The exact role of cytoplasmic and nuclear oncoproteins in mediating radiosensitivity changes in recipient cells is not known but probably represents an indirect rather than direct effect on DNA repair enzyme activity.

A schematic diagram outlining a conjectured, biochemical cascade for oncogenes thought to be correlated with radiation survival is seen in Figure 2. Membrane tyrosine kinases such as growth factor receptors can interact with submembrane proteins such as $p21^{ras}$. Aberrant mutant $p21^{ras}$ can increase secondary messages through signal transduction to other cytoplasmic oncoproteins such as the serine/threonine kinase product of the *c-raf* gene, which has been shown to be truncated and amplified in radioresistant lines. Increased message or kinase activity from extranuclear oncoproteins can then interact with nuclear proteins such as *c-myc, jun, fos* and *p53*. The exact biochemical functions of these proteins is unknown, but: (i) the *c-myc* protein can be induced by low radiation doses and has been implicated with chromatin structure; a factor known to influence sensitivity of cells to radiation damage[28]; (ii) mutant *p53* is known to complex with wild-type *p53* in a heterodimer, perhaps depleting out the suppressive effects of wild-type *p53* and thereby increasing the proportion of cells into S phase (a more radioresistant phase[13,29,30] and (iii) irradiation and chemotherapeutic drugs can inhibit *p34* kinase, a G2/M cell cycle-phase protein which could affect the duration of G2 and the time for repair of DNA damage before the onset of mitosis[4,9,11,31,32]. In addition, recent experiments have also shown that irradiation of cells will increase the expression of the nuclear *jun/fos* proteins, leading to an increased activity of the AP-1 transcriptional regulating complex, a final target of the $p21^{ras}$ pathway (Weichselbaum, R; presented at the American Society for Therapeutic Radiology and Oncology, Oct. 1990, Miami)[11].

**Table 1b: Location and Function of Selected Tumour Suppressor Genes***

| Suppressor Gene | Protein Location | Biochemical Function |
|---|---|---|
| *RB* | NUCLEAR PHOSPHOPROTEIN | GO/G1- S PHASE CONTROL |
| *WILD TYPE P53* | NUCLEAR PHOSPHOPROTEIN | GO/G1-S PHASE CONTROL |
| *K-REV-1* | CYTOPLASMIC GTP BINDING | COMPETES WITH P21 RAS FOR GAP? |
| *NM23* | NUCLEOTIDE DIPHOSPHATE KINASE | NTP SYNTHESIS, GTP BINDING INTERACTIONS |

* (DATA EROM REEERENCES: 7,9,25,30,37,43,44,48)

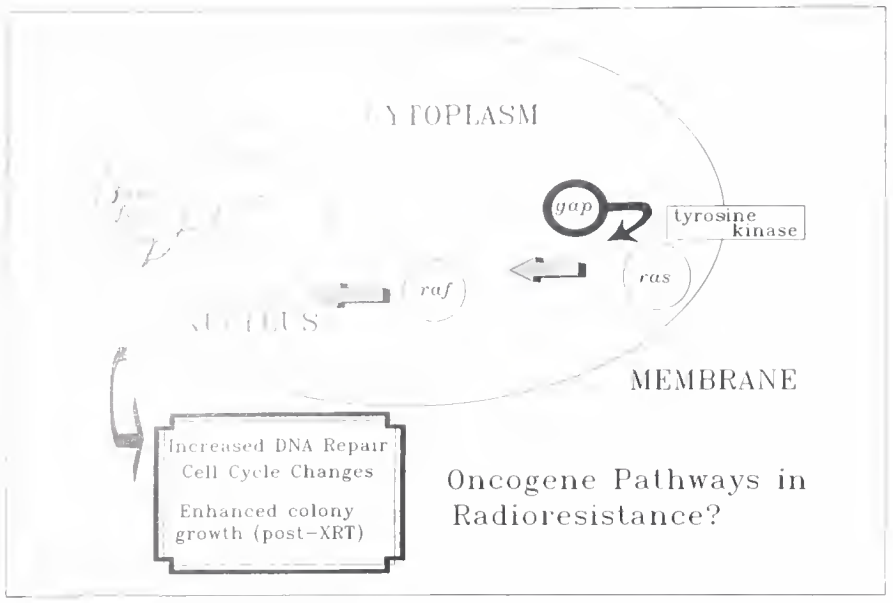



*Figure 2: Summary of proposed inter-relationships between various cytoplasmic and nuclear oncogenes reported to affect in vitro radiosensitivity of murine and human tumour cells.*

Without positive correlations between oncogene expression and proteins involved in DNA repair or increased radiation survival, pathways involved in ionizing radioresistance remain open to conjecture and definitive experimentation. Whether such differences in oncogene expression will predict for radioresistant tumours awaits the results from solid tumour biology, and subsequent one to one correlations between molecular expression and clinical radioresponse through clinical trials.

## *ONCOGENES AND METASTASIS*

Clinically, mortality associated with cancer is due to the tumour burden attributed to secondary cancer sites rather than effects from the primary tumour. The process of metastasis is an inefficient one in that the primary tumour may shed many individual cells into the host circulation, yet only a fraction of these will form secondary growths. There are many steps in the metastatic cascade; tumour cells from the primary site must detach and invade the vasculature/lymph systems, survive their transport in the host circulation and evade immune defenses, aggregate and arrest at a new location, extravasate into the surrounding parenchyma and finally undergo proliferation at the secondary site[4].

Whether these processes are random within or specific to a tumour cell sub-population is currently under considerable debate[1,2,33,34]. In that tumour cell populations are thought to be inherently genetically unstable, the metastatic phenotype may be a transient one whereby it's generation or reversion may be dependent on many genetic or environmetal factors[3]. Hill and associates[1,35] have described this instability in terms of a "dynamic heterogeneity" model of metastasis. If true, this hypothesis would suggest that putative metastatic genes ("metastogenes") may be difficult to discern as they are only being expressed at a certain time during an individual tumour cell's lifetime.

Recent genetic investigations involving transfection procedures and metastatic end-points have tried to address the role of oncogene (ie. *ras, myc, E1a*) or tumour suppressor gene (ie. *p53, nm23*) expression in determining a recipient cell line's propensity to acquire tumorigenic and/or metastatic properties. The results of many such studies using a variety of recipient cells have, in general, supported the idea that expression of the $p21^{ras}$ affects the metastatic efficiency of a given transfectant line and have indicated that the presence of other oncogene products (ie. *myc*, mutant *p53* or *E1a*) may modulate this result[36-38]. Studies of clonal populations of H-ras transfectants have demonstrated that such populations exhibit different levels of expression of $p21^{ras}$ and that these levels are correlated with metastatic potential[39,40]. Thus, the most aggressive and invasive *H-ras* transfected cells were those which showed the highest $p21^{ras}$ expression. Furthermore, it has been demonstrated that $p21^{ras}$ expression can increase expression of proteases which might be involved in the destruction of basement membranes, a step which is crucial to the metastatic process. Transfection of *E1a* into *ras*-transformed cells, which abrogates the increased metastatic potential (but not tumorigenicity), also reduces the level of protease secretion[34,39].

An explanation for direct $p21^{ras}$ involvement in tumorigenicity concerns the finding of a ras responsive transcription element which has been detected in the promoter regions of other genes involved in the metastatic phenotype (such as collagenase)[38]. Increased expression of another oncogene, *N-myc*, has been correlated with increased metastatic ability in human neuroblastoma

**Table 2**
**Summary of Radioniologic and Tumorigenic Characteristics of Primary Rat Embryo Fibroblasts Transfected with H-ras or Co-Transfected with Nuclear Oncogences**

| Genes Transfected | Radioresistance | Tumorigenic | Metastatic | |
|---|---|---|---|---|
| | | | Spontaneous | Experimental |
| *NONE (untransfected REF)* | - | - | - | - |
| *Neo marker* | +/- | - | - | - |
| *H-ras/neo* | ++/- | ++/- | + | ++ |
| *mutp53/neo* | ++ | ++ | + | + |
| *H-ras/c-myc/neo* | ++++ | ++ | + | + |
| *H-ras/E1a/neo* | +/- | + | - | - |
| *H-ras/mutp53/neo* | +++ | ++ | + | + |

These data compiled from Pardo FS, Bristow RG, Kley N. *et al.* Int. J Rad. Oncol. Biol. Phys., submitted Oct. 1990 McKenna et al.[14]

and in a transfected rat neuroblastoma cell line. In this cell line, increased *N-myc* expression was also correlated with decreased expression of MHC Class 1 antigens and of N-CAM, a cell adhesion molecule, perhaps leading to cellular detachment and evasion of MHC-restricted anti-tumour immune responses[41].

Steeg and co-workers have recently described a series of experiments in which decreased metastasis in these tumours was associated with increased RNA expression of the gene product of *nm23*, as a possible metastasis suppressor gene in murine and human tumours[10,12]. This gene has extensive homology to a homeobox gene (*awd*) in Drosophila development and encodes a nucleoside diphospate kinase (NDP) implicated in nucleoside triphosphate synthesis and GTP-binding proteins[42]. In fact, it has been shown that the effect of *E1a* in decreasing the metastatic efficiency of a *ras*-transfected line was also associated with increased expression of the *nm23* gene product[43]. The interaction between *nm23* and oncoproteins awaits the development of a monoclonal antibody against the *nm23* protein. A diagnostic assay for *nm23* expression may prove valuable in assessing the likelihood that an individual patient's tumour may metastasize.

## *SUMMARY OF TRANSFECTION RESULTS:*

Table 2 shows a summary of the available data from various laboratories including our own concerning the phenotypes seen after oncogene transfection into recipient REF cells. These results support a role for radioresistance induction with ras plus the cooperating oncogenes *c-myc* and mutant *p53* (see Figure 1b). Interestingly, *ras* plus *E1a* transfectants were radiosensitive and REF cells transfected with solely the neomycin marker (controls) may have increased radioresistance over the untransfected REF cells. This latter control had not been previously reported and suggests that part of the purported oncogene effect on radioresistance may actually be due to the transfection procedure itself and not the oncogene. Increased genetic instability of host cells may follow insertion of plasmid sequences into DNA, possibly increasing baseline DNA repair processes or directly affect radiation response due to the effects on genes located at the site of insertion. Consistent site-specific *H-ras* insertion following transfection into REF genomic DNA has been reported on long arm of rat chromosome 3[14].

The metastatic capability of REF oncogene transfectants supports that *ras* and mutant *p53* oncogenes can be dominant tumorigenic and metastatic genes under certain conditions. Co-transfected *E1a* sequences decrease the metastatic phenotype induced by *ras*, which parallels this gene's effect on radioresistance. Thus, for the transfectant categories shown, the data generally support a correlation between acquisition of metastatic potential and radioresistance.

## *CONCLUSIONS:*

Transfection of DNA into host cells confers an immediate genotype which is in direct contrast to tumour progression *in vivo* in which tumour cell populations are thought to evolve through step-wise genetic/environmental selection pressures. Thus, results from transfection studies may not predict the relative expression of oncoproteins within spontaneous human tumours or even in transplantable solid tumour models. As alluded to earlier, there is also some concern regarding the effects of the transfection procedure itself on the radioresistant and metastatic phenotypes observed. Both Kerbel *et al.*[44] and Muschel[45] have warned about interpretation of transfection results in view of induction or modulation of phenotypes by transfection phenomena or insertional effects rather than because of oncogene expression per se.

To date, there has been little data on the expression of endogenous oncogene products in solid tumours growing *in vivo*, and whether such expression is under the influence of microenvironmental factors. An example of a parameter which may affect tumour cell properties is the degree of tumour oxygenation. The levels of intra-tumour hypoxia which increase with tumour size and the number of tumour cells experiencing hypoxic conditions ranges from less than 10% to up to 50% of the total tumour cell population[46]. Hill and his associates have demonstrated that following reoxygenation, cells which were isolated from hypoxic regions of tumours using fluorescence-activated cell sorting, differ in a number of characteristics including: proliferative rate, cell cycle phase, normal replication of DNA, and have a metastatic efficiency twice that of cells found in more oxygenated regions[47-49]. These observations may have important clinical implications as it is also these hypoxic cells which are refractory to radiation and drug treatments. Environmental or therapeutic influences might lead to the selection of cells with increased oncogene expression and enhanced metastasis. Intuitively, a minimum threshold of expression would be needed by one or more oncoproteins by a significant number of cells within a tumour cell population before a specific aggressive or resistant phenotype is observed.

The question still remains whether results of oncogenic expression studies in human tumours will prove useful for predicting treatment response. Hopefully, tumours containing therapeutically resistant cells may be identified at an early stage, allowing modifications or additions to standard regimens that are likely to fail given the inherent biology of the tumour. Whether aggressive tumour cell variants capable of self-renewal are associated with defined oncogenetic changes remains to be proven. Such variant cells would begin to fulfill the criteria of the hypothesized tumour "stem" cell; the target of all cancer therapies and the knowledge about the properties of which, constitute the clinical oncologist's holy grail.

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## REFERENCES


1. Hill RP, Chambers AF, Lundy J, Harris J. Dynamic Heterogeneity: rapid generation of metastatic [illegible] in mouse B16 melanoma cells. Science 1984; 224: 998-1001.
2. Nicolson G. Tumor [illegible] oncogenes and the evolution of metastatic phenotype [illegible]. Clin. Exp. Metastasis 1984; 2: 85-105.
3. Nowell P. The clonal evolution of tumour cell populations. Science 1976; 194: 23-28.
4. Liotta L. Gene products which play a role in cancer invasion and metastasis. Breast Can. Res. Treat. 1988; 11: 113-124.
5. Muschel R, Liotta L. Role of oncogenes in metastasis. Carcinogenesis 1988; 9: 705-710.
6. Weiss L, Orr F, Honn K. Interactions between cancer cells and the microvasculature: a rate-regulator for metastasis. Clin. Exp. Metastasis 1989; 7: 127-167.
7. Peters G. Oncogenes at viral integration sites. Cell Growth and Diff. 1990; 1:503-510.
8. Hinds PW, Finlay C, Levine A. Mutation is required to activate the *p53* gene for cooperation with the ras oncogene and transformation J. Virol. 1989; 63:739-746.
9. Ruley HE. Transforming Collaborations between *ras* and nuclear oncogenes. Cancer Cells 1990; 2: 258-268.
10. Liotta L, Steeg P. Clues to the Function of *nm23* and *Awd* proteins in development, signal transduction, and tumour metastasis provided by studies of dictyostelium discoideum. J. Nat. Cancer Inst. 1990; 84:170-172.
11. Pawson T. Biochemistry of the cancer cell. Curr. Opinion in Oncol. 1990; 2:143-151.
12. Sobel M. Metastasis Suppressor Genes. J. Nat. Cancer Inst. 82: 267-276, 1990.
13. Finlay C, Hinds PW, Levine A. The *p53* proto-oncogene can act as a suppressor of transformation. Cell 1989; 57:1083-1093.
14. McKenna WG, Weiss M, Bakanaukas V, Sandler H. *et al.* The role of the H-ras oncogene in radiation resistance and metastasis. Int. J. Rad. Oncol. Biol. Phys. 1990; 18:849-859.
15. Sinn E, Muller W, Pattengale *et al.* Co-expression of MMTV/*v-Ha-ras* and MMTV/*c-myc* genes in trangenic mice: Synergistic action of oncogenes *in vivo*. Cell 1987; 49: 465-475.
16. Hill RP, Milas L. The proportion of stem cells in murine tumours. Int. J. Rad. Oncol. Biol. Phys. 1989; 16: 513-518.
17. Bristow RG, Hardy P, Hill RP. Comparison between *in vitro* radiosensitivity and *in vivo* radioresponse of murine tumour lines I: Parameters of *in vitro* radiosensitivity and endogenous cellular glutathione levels. Int. J. Rad. Oncol. Biol. Phys. 1990; 18:133-145.
18. Peters LJ, Brock W, Johnson A, Meyn R, Tofilon P, Milas L. Potential Methods for predicting tumour radiocurability. Int. J Rad. Oncol. Biol. Phys. 1986; 12: 459-467.
19. Fertil B, Malaise EP. Intrinsic Radiosensitivty of human tumour lines is correlated with radioresponsiveness of human tumours: a study based on 101 published survival curves. Int. J. Rad. Oncol. Biol. Phys. 1985; 11:1699-1701.
20. Bristow RG, Hill RP. Comparison between *in vitro* radiosensitivity and in vivo radioresponse of murine tumour lines II: *In vivo* radioresponse after fractionated treatment and *in vitro/in vivo* correlations. Int. J. Rad. Oncol. Biol. Phys. 1990; 18:331-345.
21. Hoeijmakers J Bootsma D. Molecular genetics of eukaryotic DNA excision repair. Cancer Cells 1990; 2: 311-320.
22. Sklar M. Increased resistance to cis-Diaminodichloroplatinum(II) in NIH 3T3 cells transformed by *ras* oncogenes. Cancer Research 1988; 48:793-797.
23. Sklar M. The *ras* oncogenes increase the intrinsic resistance of NIH 3T3 cells to ionizing radiation. Science 1988; 239:645-647.
24. Harris JF, Chambers AF, Tam A. Some *ras*-transformed cells have increased radiosensitivity and decreased repair of sublethal radiation damage. Somatic Cell. Mol. Gen. 1990; 16:39-48.
25. Grant ML, Brunton RK, Byrd PJ, Gallimore PH, Steele JC, Taylor AMR , Grand RJ. Sensitivity to ionizing radiation of transformed human cells containing mutant *ras* genes Oncogene 1990; 8: 1159-1164.
26. Kasid U, Pfeifer A, Brennan T, Brackett M, Weichselbaum R, Dritschilo A, Mark G. Effect of antisense *c-raf-1* on tumorigenicity and radiations sensitivity of a human squamous cell carcinoma. Science 1989; 243: 1354-1356.
27. Chang EH, Pirollo KF, Zou ZQ, Cheung HY, Lawler EL, Garner R, White E, Bernstein WB, Fraumeni JW, Blattner WA. Oncogenes in radioresistant, noncancerous skin fibroblasts from a cancer-prone family. Science 1988; 237: 1036-1039.
28. Sullivan N., Willis A. Elevation of *c-myc* protein by DNA strand damage. Oncogene 1989; 1497-1502.
29. Diller L, Kassel J, Nelson C, Gryka M, Litwak G, Gebhardt M, Bressac B, Ozturk M, Baker S, Vogelstein B, Friend S. *p53* functions as a cell cycle control protein in osteosarcomas. Mol. Cell. Biol. 1990; 10:5772-5781.
30. Lane D. Benchimol S. *p53*: Oncogene or anti-oncogene? Genes and Development 1990; 4: 1-8.
31. Addison C, Jenkins J, Sturzbecher H. The *p53* nuclear localization signal is structurally linked to a *p34cdc2* kinase motif. Oncogene 1990; 3; 423-426.
32. Prives C. The replication functions of SV40 T antigen are regulated by phosphorylation. Cell 1990; 61:735-738.
33. Cifone M, Fidler I. Increasing metastatic potential is associated with increasing genetic instability of clones isolated from murine neoplasms. Proc. Nat. Acad. Sci. (USA) 1981; 78: 6949-6952
34. Pozzatti R, McCormick M, Thompson M, Khoury G. The *Ela* gene of adenovirus type 2 reduces the metastatic potential of *ras*-transformed rat embryo cells. Mol Cell. Biol. 1988; 8: 2984-2988.
35. Hill RP, Young S, Cillo C, Ling V. Metastatic cell phenotypes: Quantitative studies using the experimental metastasis assay. Cancer Rev. 1986; 5:118-151.
36. Ananthaswamy HJ, Price J, Tainsky M, Goldberg L, Bales E. Correlation between *Ha-ras* gene amplification and spontaneous metastasis in NIH 3T3 cells transfected with genomic DNA from human skin cancers. Clin. Exp. Metastasis 1989; 7:301-313.
37. Pohl J, Goldfinger N, Radler-Pohl A, Rotter V, Shirmacher V. *p53* increases experimental metastatic capacity of murine carcinoma cells. Mol. Cell. Biol. 1988; 8: 2078-2081.
38. Wright JS, Egan S, Greenberg A. Genetic Regulation of Metastatic Progression. Anticancer Res. 1990; 10: 1247-1256.
39. Chambers AG, Denhardt S, Wilson S. *Ras*-transformed NIH 3T3 cell lines, selected for metastatic ability in chick embryos have increased proportions of *p21*-expressing cells and are metastatic in nude mice. Invasion Metastasis 1990; 10: 225-240.
40. Hill SA, Wilson S, Chambers AF. Clonal heterogeneity, experimental metastatic ability and p21 expression in *Ha-ras*-transformed NIH-3T3 cells. J. Natl. Cancer Inst. 1988; 80:484-490.
41. Akeson R, Bernards R. *N-myc* down regulates neural cell adhesion molecule expression in rat neuroblastoma. Mol. Cell. Biol. 1990; 10:2012-2016.
42. Wallet V, Mutzel R, Troll H, Barzu O, Wurster W, Veron M, Lacombe M. Dictostelium nucletide diphosphate kinase highly homologous to *nm23* and *Awd* proteins involved in mammalian tumour development and Drosophila development. J. Nat. Can. Instit. 1990; 82: 1199-1202.
43. Steeg PS, Bevilacqua G, Pozzatti R, Liotta L, Sobel M. Altered Expression of *nm23*, a gene associated with low tumour metastatic potential during adenovirus 2 *E1a* inhibition of experimental metastasis. Cancer Res. 1988; 48:6550-6554.
44. Kerbel R, Waghorne C, Man M, Elliot B, Breitman M. Alteration of the tumorigenic and metastatic properties of neoplastic cells is associated with the process of calcium phosphate-mediated DNA transfection. Proc. Nat. Acad. Sci. (USA) 1983; 84:1263-1267.
45. Muschel R. Selection for spontaneous metastasis after calcium phosphate-mediated transfer of DNA. Cancer Res. 1990; 50: 5581-5586.
46. Moulder J, Rockwell S. Tumor hypoxia: its impact on cancer therapy. Cancer Metastasis Rev. 1987; 5: 313-341.
47. Young SD, Marshall RS,Hill RP Hypoxia induces DNA overreplication and enhances the metastatic potential of murine tumour cells. Proc. Nat. Acad. Sci. (USA)1988; 85:9533-9537.
48. Young SD, Hill RP. Effects of reoxygenation on cells from hypoxic regions of solid tumours: Analysis of transplanted murine tumours for evidence of DNA overreplication. Cancer Res. 1990; 50: 5031-5038.
49. Young SD, Hill RP. Effects of reoxygenation on cells from hypoxic regions of solid tumours: Anticancer drug sensitivity and metastatic potential. J. Nat. Cancer Inst. 1990; 82: 371-380.

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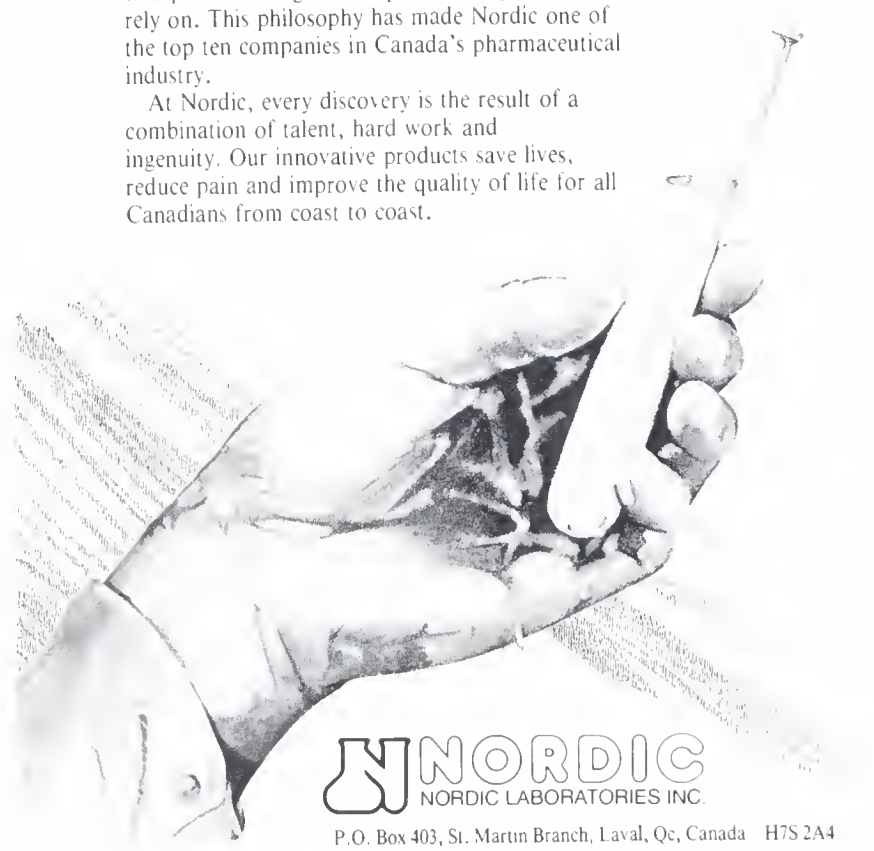

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# Functional Neuroimaging: Technetium 99m Hexamethyl-Propyleneamine Oxime and Single Photon Emission Computed Tomography in the Differential Diagnosis of Dementia

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ABSTRACT

**Single Photon Emission Computed Tomography (SPECT) is a functional imaging technique capable of assessing various physiological parameters such as regional cerebral blood flow. The recent development of technetium 99m hexamethyl-propyleneamine oxime ([99m-Tc]HM-PAO), a lipophilic agent which, upon intravenous injection, crosses the blood brain barrier and is retained in the brain parenchyma in proportion to cerebral perfusion, has opened up new possibilities for functional imaging of neurodegenerative processes. [99m-Tc]HM-PAO SPECT is rapid, non-invasive, and cost-effective, with an excellent potential in aiding the differential diagnosis of dementia by providing an objective measure of brain function which can complement and extend clinical judgement.**

ABSTRAIT

**Le SPECT (tomographie à calculateur intégré avec émission de photons simples) est une technique de visualisation functionnelle avec laquelle il est possible d'évaluer divers paramêtres physiologiques, comme example le débit cérébral régional. En plus, le développment récent de la substance technétium 99m hexaméthyl-propylèneamine oxime ([99m-Tc]HM-PAO), un agent lipophile qui après l'injection intraveineuse croise la barrière hémato-encéphalique et demeure dans la parenchyme du cerveau en proportion avec sa perfusion sanguine, offre des nouvelles possibilités d'imagerie pour les processus neurodégénératifs. Une technique rapide, non sanglante et rentable, le [99m-Tc]HM-PAO SPECT a le potentiel d'aider le diagnostic différentiel de la démence en permettant une mesure objective des functions cérébrales devenant ainsi un ajout complémentaire aux impressions cliniques.**

## *INTRODUCTION TO FUNCTIONAL NEUROIMAGING*

Probing the relationship between the mind and the brain is perhaps one of the most important and exciting scientific challenges in medicine today. One approach to meeting this challenge has been the development of modern neuroimaging tools which can be divided into two broad categories, structural and functional (Fig. 1). Structural techniques include X-ray Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) and both are used for visualizing brain anatomy. Clinically, CT has the ability to assess cortical atrophy, ventricular dilatation, neoplastic

*Figure 1. Conceptual difference between functional and anatomical neuroimaging.*

changes and cerebrovascular disease based on serial transaxial images of the brain. In contrast, MRI obviates the need for ionizing radiation, allows for the exquisitely detailed imaging of the brain in transaxial, coronal and sagittal planes, and is also very sensitive for the detection of focal white matter lesions[1].

Whereas CT and MRI have greatly aided our understanding of neuroanatomy, it is often brain metabolism and variations in brain activity in response to environmental insults which are of primary concern. Currently the three major functional techniques for studying the brain include computerized brain electrical activity mapping (BEAM) for analyzing brain wave patterns, positron emission tomography (PET), and single photon emission computed tomography (SPECT). The advantage of PET over the anatomic imaging modalities is that derivatives of carbon, oxygen, and other biologically relevant atoms, can be incorporated into molecules for imaging regional cerebral blood flow (rCBF), oxygen/glucose metabolism, and protein synthesis. More recently, neurotransmitter/neuroreceptor systems have also been

imaged. Thus PET, with its ability to bridge the gap between behavior and brain chemistry, has firmly established itself as the premier research tool for assessing cerebral metabolism[2].

However, the evolution of SPECT as a neuroimaging modality has not been lagging far behind. It is a method for assessing the three-dimensional distribution of a radioactive pharmaceutical compound within the human body, and recent advances in SPECT methodology have greatly improved parameters such as spatial resolution, sensitivity of radioactivity detection, as well as speed of data acquisition. Coupled with the development of radiopharmaceuticals for measuring cerebral blood flow and determining the distribution of selected neurotransmitter/neuroreceptor systems, SPECT has become a means to translate the research capabilities of PET into modern clinical practice. The attractiveness of SPECT over PET instrumentation resides in more practical considerations such as much lower acquisition and maintenance costs, ease of operation, and ready availability in most nuclear medicine facilities[3].

The following is a brief and selective overview of SPECT as an increasingly important neuroimaging modality in general and its role in the differential diagnosis of dementia in particular.

## *SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY*

In conventional radionuclide imaging, the tracer of choice is injected intravenously and a detecting device such as a gamma camera is used to collect the photon emission. The data obtained is amplified and projected onto photographic film, resulting in an image which is purely two-dimensional in nature. No information is obtained regarding the depth of emitting isotopes within the anatomical structure of interest. Although it is possible to image from multiple angles to achieve greater localization in three dimensions, the length of time required to obtain the additional data and the proliferation of images to be viewed represent a practical constraint on this approach. A more serious drawback is that each image represents the sum total of activity through the full thickness of the object. This causes a direct reduction of contrast in the image by overlying and underlying tissues. In neuroimaging, this attenuation effect is of particular concern given the small size and great complexity of the brain[4].

**TABLE I**
**ADVANTAGES OF SPECT OVER PLANAR IMAGING**

- TRUE 3-D POSITIONAL INFORMATION FOR IMPROVED LOCALIZATION OF LESIONS
- REMOVAL OF OVERLYING/UNDERLYING TISSUE ACTIVITY FOR IMPROVED IMAGE CONTRAST
- QUANTITATION OF RADIO-TRACER UPTAKE FOR MEASURING PHYSIOLOGICAL PARAMETERS

SPECT represents a logical extension of multi-view imaging. Here the data are acquired using a gamma camera which rotates a full 360° around a stationary patient. In our facility, 60 views (every 6°) are collected, and the data are mathematically reconstructed to form images in any plane of the body. However, the transaxial, sagittal, and coronal views are most commonly used for image interpretation.

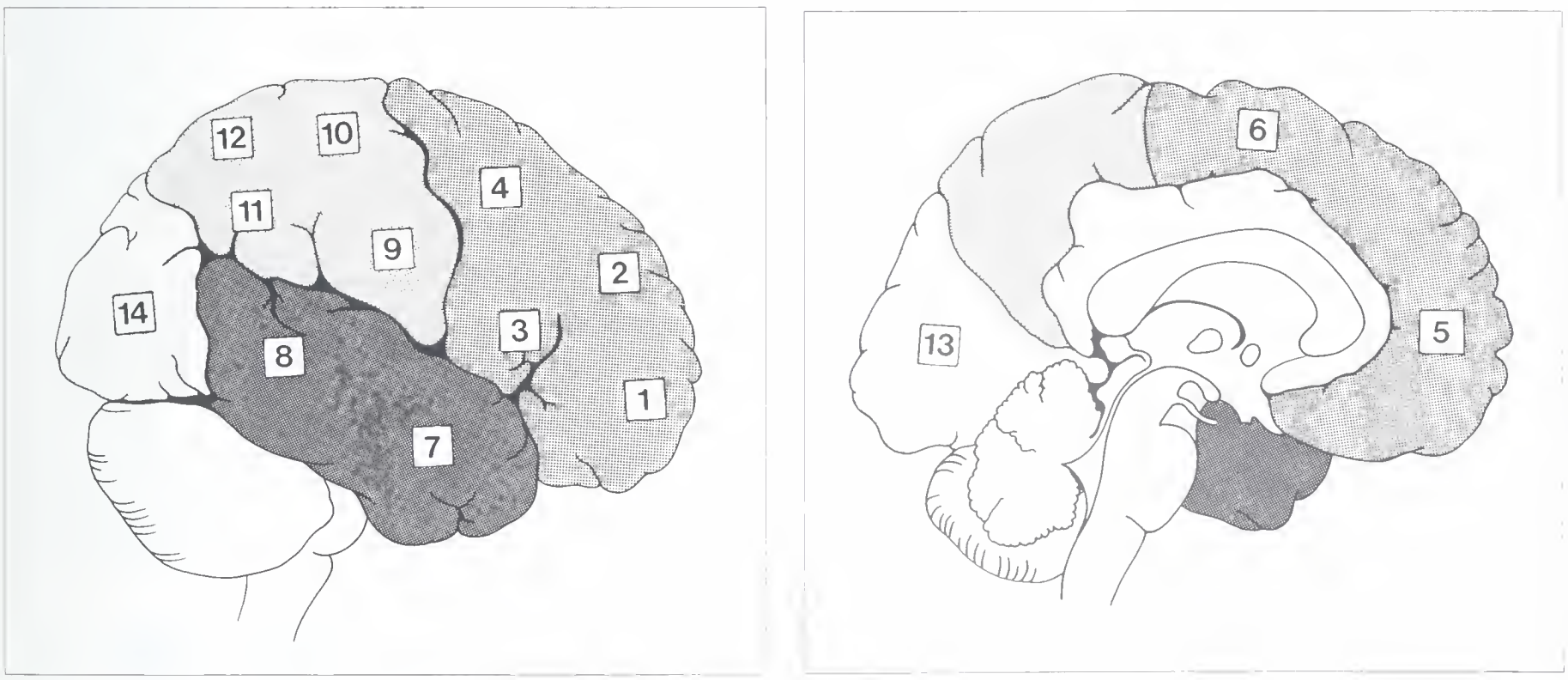


*Figure 2. Surface map showing the segmental neuroanatomical divisions employed for visual SPECT scan analysis and relative quantitation of regional cerebral blood flow. Frontal Lobe:1. anterior inferior frontal, 2. anterior superior frontal, 3. posterior inferior frontal, 4. posterior superior frontal, 5. medial inferior frontal, 6. medial superior frontal. Temporal Lobe: 7. anterior inferior temporal, 8. posterior superior temporal. Parietal Lobe: 9. anterior inferior parietal, 10. anterior superior parietal,11. posterior inferior parietal,12. posterior superior parietal. Occipital Lobe:13. medial occipital, 14. lateral occipital. Basal Ganglia:15. basal ganglia.*

Although the acquisition time for each individual view is short and thus the image quality is poor, the data reconstruction process offsets this problem and offers specific advantages over conventional planar imaging as outlined in table 1. The data are normally viewed as a series of multiple two-dimensional images with each occupying a different position in the third dimension. This results in superior functional information with improved localization of lesions. In addition, the attenuation of activity from interfering (i.e. overlying and underlying) tissues is removed to a large extent, leading to much improved contrast in these SPECT images. Although it is difficult to obtain absolute values of blood flow in ml per minute per unit weight of brain tissue, a third advantage is that cortical perfusion of a particular region of interest can be expressed relative to a second area such as the cerebellar perfusion which is generally spared in diseases such as Alzheimer's dementia[6].

## *CLINICAL APPLICATIONS OF SPECT IMAGING*

SPECT studies on the distribution of radiolabeled agents have been of diagnostic value in a wide variety of clinical conditions. Excellent progress has been made in the areas of myocardial perfusion imaging using thallium 201, technetium 99m labeled red blood cells, and more recent agents such as technetium 99m labeled monoclonal antibody against activated platelets for visualizing occlusive arterial thrombi[3,7]. SPECT has also seen extensive application in the imaging of lymphomas, hemangiomas and other focal lesions of the liver, as well as abnormalities in bone metabolism[3].

However, some of the most significant advances have been made in SPECT imaging of the central nervous system. The monitoring of blood rCBF has been of prime interest since flow has been shown to be directly coupled to oxygen consumption and glucose metabolism[8]. Xenon133 inhalation studies have been used to monitor rCBF, but are of limited value due to poor spatial resolution and the high radiation doses necessary for imaging. In contrast, lipophilic radiopharmaceuticals such as iodine 123 labeled N-isopropyl-p-iodo-amphetamine (IMP) and N,N,N-trimethyl-N-[2-hydroxyl-3-methyl-5-iodo-benzyl]-1,3-propanediamine (HIPDM) can cross the blood brain barrier and are retained in the brain tissue either by binding to nonspecific receptors or by conversion to non-lipophilic compounds. These two tracers have seen extensive clinical use in a variety of neurological disorders including the dementias. However, iodine 123 isotopes need to be cyclotron generated in order to avoid contamination by higher energy emitting iodine 124 which can cause image degradation due to increased photon scatter[9]. This limits the availability of pure iodine 123 compounds in routine clinical practice.

The recent introduction of [Tc-99m]HM-PAO as an agent for monitoring rCBF has greatly increased the utility of SPECT as a functional neuroimaging modality. [Tc-99m]HM-PAO is also a lipophilic molecule which crosses the blood brain barrier. It is virtually completely cleared from the blood in a single pass through the cerebral circulation and its regional distribution and uptake within the brain parenchyma can be considered to be proportional to rCBF. Furthermore, [Tc-99m]HM-PAO does not suffer from the same type of limitations as the iodine 123 labeled compounds and is readily available from commercial distributor. Since its activity remains fixed in the cerebral cortex, delayed equilibrium SPECT imaging can be performed and tracer redistribution does not complicate the interpretation of the data[10,11].

From the discussion above it is clear that SPECT imaging employing different radiopharmaceuticals is essential in the diagnosis and follow-up of a wide variety of clinical entities. The current efforts directed at developing newer and more specific tracer compounds will only increase the already significant contribution of SPECT methodology to modern diagnostic medical imaging.

## *METHODOLOGY: SUBJECTS*

The subjects for the illustrative rCBF SPECT studies shown below were recruited from patients referred for the assessment of dementia to the Behavioral Neurology program at Baycrest Hospital, Toronto. Informed consent was obtained and their clinical diagnoses (made independently of the SPECT scan results) were based on bedside tests of memory, language, ideomotor praxis, visuospatial performance, manipulation of acquired knowledge, and frontal lobe function.

## *[Tc-99m] HM-PAO SPECT IMAGING*

Each subject was given 500 mg sodium perchlorate p.o. to prevent salivary gland uptake of the radiopharmaceutical. This was followed by an injection of 740 MBq [Tc-99m]HM-PAO i.v.. Brain SPECT studies were performed 15 min later using Elscint AG 409 rotating gamma camera instrumentation. Patients were placed supine with the camera face perpendicular to the subjects' cantho-meatal line. Images were obtained through 360 degrees of rotation with a high resolution parallel hole collimator. The data were acquired on a 64 x 64 matrix, normalized to byte mode, and corrected for non-uniformity. Transaxial images were recon-

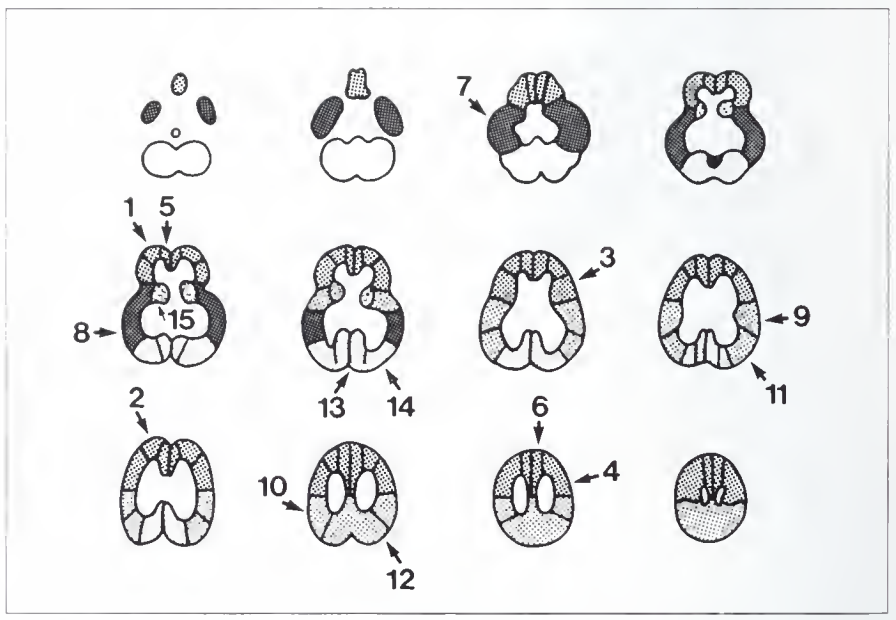


*Figure 3. Segmental neuroanatomical divisions used for the interpretation and quantitation of transaxial SPECT images.*

structed using a modified Hanning back projection filter with attenuation correction (0.04 cm-1, Chang Method) and a magnification zoom of 1.8. Coronal and sagittal views were reconstructed from the transaxial images and all three sets were visually interpreted without the benefit of the clinical diagnoses.

## *DATA ANALYSIS*

Identification of neuroanatomical regions was based on a tomographic atlas of the brain (figures 2 & 3)[12]. Relative quantitation of rCBF was carried out by determining the activities represented by rectangular regions of interest (ROIs) over selected regions in the frontal, parietal, occipital and temporal lobes. Perfusion to the basal ganglia and the cerebellum was assessed as well. The average of the right and left cerebellar activities was used for normalization purposes to obtain relative cortical/cerebellar perfusion ratios. A total of 30 regional cortical/cerebellar ratios were evaluated for each SPECT study. The coefficient of variation among repeated determinations on the same subject within a single SPECT study averaged 2.5%.

## *ROLE OF SPECT IN THE DIFFERENTIAL DIAGNOSIS OF DEMENTIA*

Dementia is the most common cerebral symptom complex to afflict the middle-aged and elderly population in North America. It can be defined as an acquired, persistent, and greatly debilitating impairment of intellectual function with compromise in at least three of the following spheres of mental activity: language, memory, visuospatial skills, emotion or personality, and cognition (e.g. calculation, judgement, abstraction, etc.). It is estimated that 15% of people over the age of 65 have varying degrees of dementia. Although the differential diagnosis of dementia can encompass a multitude of neurodegenerative disorders and other etiologies, Alzheimer's disease accounts for more than 50% of cases and is present in approximately half of nursing home patients. The cost to society of providing care for these patients is estimated to be in excess of $20 billion annually. Thus Alzheimer's disease and dementia in general have a disastrous impact on patients, their families and society in general from both psychological and financial points of view[13,14].

While many patients can be classified early in their course as probable Alzheimer's disease on clinical grounds, others remain diagnostic dilemmas until their symptomatology has progressed considerably with time, or the patients have come to autopsy[15] Even though effective therapeutic measures for Alzheimer's disease do not exist at the present time, early resolution of diagnostic dilemmas is clearly desirable since there are other etiologies which represent reversible forms of dementia amenable to medical intervention.

## *ILLUSTRATIVE EXAMPLES OF SPECT IMAGING IN DEMENTIA*

In the normal control subject, there is homogenous uptake of [Tc-99m]HM-PAO in the cortical grey matter, decreased uptake in the white matter due to lesser perfusion, and no uptake in the ventricles (figure 4). The greatest degree of uptake is seen in the occipital area since injection of the radiopharmaceutical was performed with eyes open.

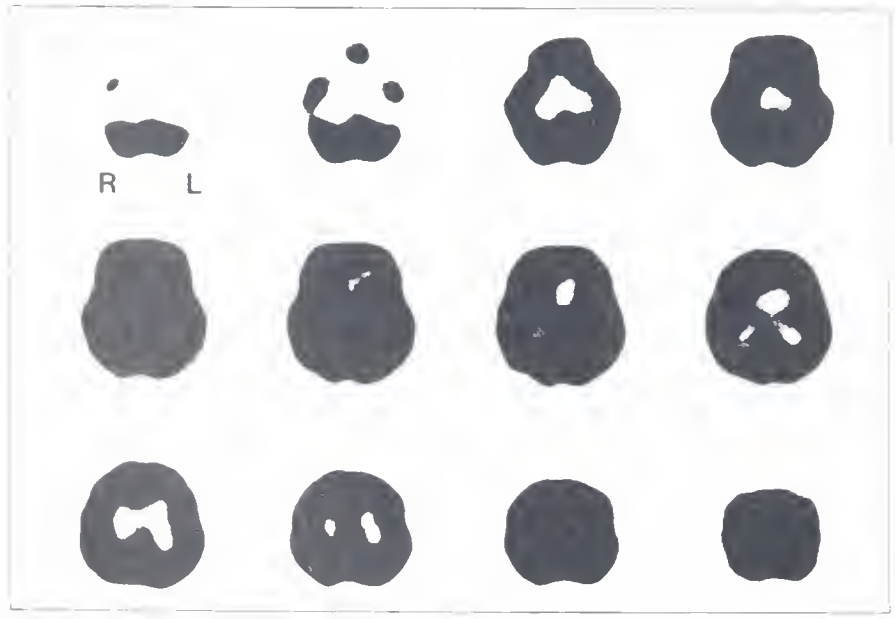


*Figure 4. Homogenous and symmetrical perfusion in a 48 year old male normal control subject.*

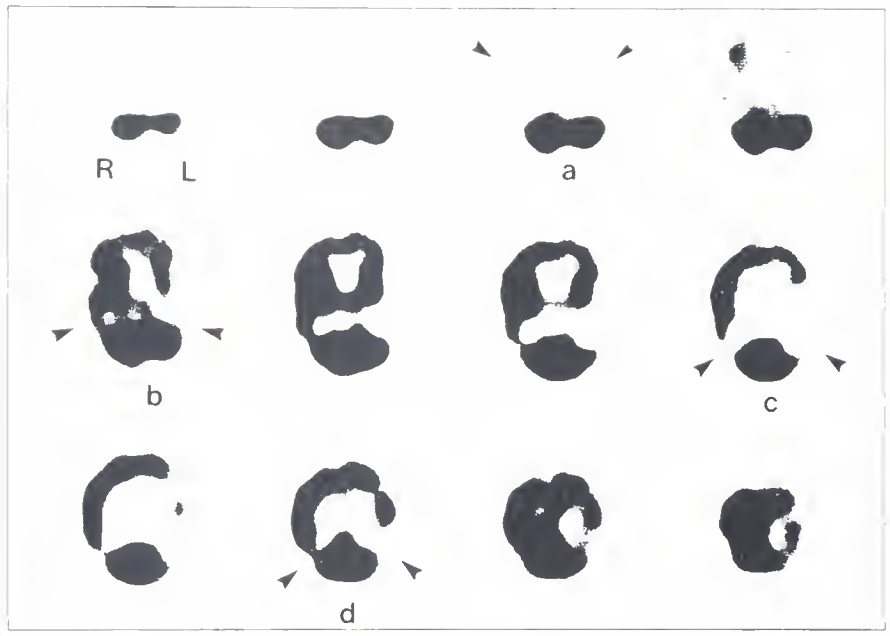


*Figure 5. Temporal (a,b) and parietal (c,d) lobe perfusion deficits in a 64 year old male dementia patient with a clinical diagnosis of Alzheimer's disease.*

In the case of Alzheimer's disease, PET and SPECT scans have generally demonstrated hypoperfusion of the posterior temporoparietal regions[2-5,13,16-19]. Figure 5 shows a [Tc-99m]HM-PAO SPECT scan of a 64 year old male with bilateral cortical rCBF deficits in the temporal lobes and extending into the parietal lobes. The sensitivity and reproducibility of SPECT imaging was demonstrated in the follow-up scan of this patient 16 months later which showed clear progression of the perfusion deficits observed on initial examination (data not shown). Recently, other types of perfusion patterns involving the frontal lobes in addition to the temporal and parietal regions have been reported[20]. In contrast to these findings, CT and MRI are often negative or show only nonspecific cortical atrophy and ventricular enlargement which may be the result of a normal aging process[21].

After coronary artery disease and cancer, cerebrovascular disease is the third most common cause of death in people 65 years of

age or older in North America. The reliable diagnosis of multi-infarct dementia (MID) as opposed to Alzheimer's disease could alter patient management and alleviate family concerns. MID is characterized by multiple focal perfusion deficits that correspond to areas of infarction seen on CT scans[3,4,13,15,16]. Figure 6 shows a typical perfusion pattern of an 81 year old male patient with a clinical diagnosis of MID. The scan results are clearly different from the pattern observed in the Alzheimer's patient above.

Figure 7 shows an example of the rCBF perfusion deficits observed in a 50 year old male patient with a clinical diagnosis of Pick's disease, a relatively rare cause of dementia. The pattern of frontal and anterior temporal hypoperfusion is consistent with the pathology of this disease[16,20,23]. The follow-up scan 32 months later shows marked worsening of the initially observed rCBF deficits. Of differential diagnostic value is the fact that the perfusion of the parietal lobes remains initially intact.

The value of rCBF SPECT imaging is not limited to the examples shown above. Other characteristic perfusion deficits have been observed in progressive supranuclear palsy which shows frontal lobe involvement, Huntington's disease with diffusely decreased cortical uptake in general and caudate nucleus in particular, and normal pressure hydrocephalus which exhibits diffuse cortical perfusion deficits[16,24,25]. Thus it is clear that rCBF SPECT imaging is well suited for the functional imaging of the dementias.

## *CORRELATION OF RCBF SPECT DEFICITS WITH NEUROPSYCHOLOGICAL TESTING DATA*

To further our understanding of the anatomy underlying brain-behavior relationships, attempts have been made to correlate perfusion deficits with neuropsychological testing results[19]. Although these types of studies are currently in their infancy, recent improvements in spatial resolution utilizing neuro-dedicated instruments have allowed the correlation of precise anatomical regions with a variety of cognitive deficits. Since there is no great consensus in the literature regarding this area of research, we have recently completed our own retrospective study evaluating 30 dementia patients[28], and a larger scale survey involving 100 patients is nearing completion. Despite the lack of neuro-dedicated instrumentation, it is nonetheless possible to obtain clinically useful information. Preliminary data suggest significant correlations between language and average left hemisphere hypoperfusion (with 'language' encompassing measures of word finding difficulty, confrontation naming, paraphasias and auditory comprehension), as well as between ideomotor limb praxis and the left anterior inferior portions of the frontal and parietal lobes [28]. Although much more data compilation and statistical analyses are necessary for a valid assignment of particular cognitive functions to specific anatomical locations using rCBF SPECT, this type of analysis may indeed be possible in the near future. The implications of this capability for investigating the relationship between the mind and the brain are clear.

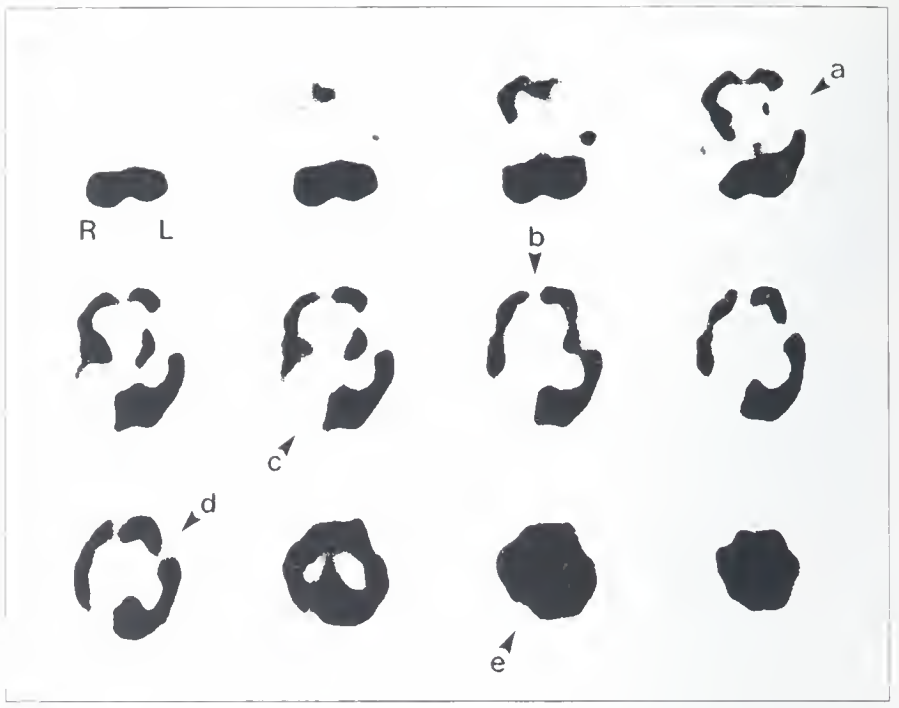


*Figure 6. Multiple perfusion deficits in the temporal (a) frontal (b,d), parietal (c) and occipital (c,e) lobes in an 81 year old male dementia patient with a clinical diagnosis of multi-infarct dementia.*

*Figure 7. Progression of a moderate left fronto-temporal (A) to a severe left fronto-temporo-parietal (B) lobe perfusion deficit in a 50 year old dementia patient with a clinical diagnosis of Pick's disease.*

## *LIMITATIONS OF rCBF SPECT IMAGING*

Despite the attractiveness of rCBF SPECT as a powerful neuroimaging technique, there are potential pitfalls and drawbacks as is the case with any other diagnostic modality. A detailed description of the technical limitations inherent in SPECT imaging is beyond the scope of this communication. However, it should be noted that this modality provides an anatomical profile of a physiological parameter. As such, SPECT imaging cannot provide a definitive diagnosis. Also, in cases where different diagnostic possibilities have identical or similar anatomical lesion sites, SPECT may be rendered incapable of contributing to the determination of etiology. Additional confounders are repre-

sented by clinical entities such as alcoholic dementia and post-anoxic encephalopathy which affect cerebellar perfusion[28]. Thus cortical/cerebellar ratios no longer provide reliable measures of rCBF deficits in these patients. In these cases SPECT will benefit from various receptor imaging agents as they become available in the future and increase the specificity of this technique.

## *CONCLUSIONS AND FUTURE DIRECTIONS*

SPECT is a practical method of functional neuroimaging in the clinical setting. The examples shown above illustrate that rCBF SPECT can provide important physiological information to aid our understanding of brain-behavior relationships and assist in the differential diagnosis of dementing disorders. In addition, functional imaging may provide greater insight into the pathophysiology of neurodegenerative diseases which will point the way towards identifying novel therapeutic options in these debilitating illnesses. Improvements in current, and discoveries of new therapeutic regimens will then extend the usefulness of SPECT to prognosis, prediction of treatment response, and indeed the serial monitoring of such response.

## *ACKNOWLEDGEMENTS*

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## *REFERENCES*

1. Andreasen NC. 'Brain Imaging: Applications in Psychiatry', Andreasen, N.C. ed., Raven Press, New York, 1989.
2. Jolles PR, Chapman PR, Alavi A. PET, CT and MRI in the Evaluation of Neuropsychiatric Disorders: Current Applications. J. Nucl. Med. 1989; 30: 1589-1606.
3. Holman BL, Tumeh SS. Single-Photon Emission Computed Tomography (SPECT). JAMA 1990; 263: 561-564.
4. Devous MD. Imaging brain function by Single-Photon Emission Computed Tomography. In 'Brain Imaging: Applications in Psychiatry', Andreasen, N.C. ed., Raven Press, New York, 1989; pp 147-234.
5. Biersack HJ, Grunwald F, Reichmann K *et al.* Functional Brain Imaging with Single Photon Emission Computed Tomography using Tc-99m labeled HMPAO. Nuc. Med. Annual 1990; 59-94.
6. Kushner M, Tobin M, Alavi A *et al.* Cerebellar Glucose Consumption in Normal and Pathologic States Using FDG and PET. J. Nucl. Med. 1987; 28:1667-1670.
7. Chouraqui P, Maddahi J, Yano J *et al.* Successful In-Vivo Visualization of Occlusive Arterial Thrombi by Tc-99m Labeled Monoclonal Antibody Against Activated Platelets. J. Nucl. Med. 1990; 31: 713.
8. Reivich M. Blood Flow Metabolism Coupling in Brain, in 'Brain Dysfunction in Metabolic Disorders, Plum F ed., Raven Press New York, 1974; pp 125-140.
9. English RJ, Holman BL. Current Status of Cerebral Perfusion Radio-pharmaceuticals. J. Nucl. Med. Tech. 1987; 15: 30-35.
10. Leonard JP, Nowotnik DP *et al.* 99m-Tc HM-PAO: A New Radio-pharmaceutical for Imaging Regional Brain Perfusion Using SPECT. J. Nucl. Med. 1986; 27: 1819-1823.
11. Podreka I, Suess E, Goldenberg G *et al.* Initial Experience with Technetium-99m HM-PAO Brain SPECT. J. Nucl. Med. 1987; 28: 1657-1666.
12. Kretschmann HJ, Weinrich W. eds. Neuroanatomy and Cranial Computed Tomography. Thieme Inc., New York, 1986.
13. Holman BL. Perfusion and Receptor SPECT in the Dementias. J. Nucl. Med. 1986; 27: 855-860.
14. Evans DA, Funkenstein HH, Albert MS. Prevalence of Alzheimer's Disease in a Community Population of Older Persons. JAMA 1989; 262: 2552-2556.
15. Gemmel HG, Sharp PF, Besson JAO *et al.* Differential Diagnosis in Dementia Using the Cerebral Blood Flow Agent 99mTc HM-PAO: A SPECT Study. J. Computer Assisted Tomography 1987; 11: 398-402.
16. Neary D, Snowden JS, Shields RA *et al.* Single Photon Emission Tomography using 99m Tc HM-PAO in the investigation of dementia. J. Neurol. Neurosurg. Psych. 1987; 50: 1101-1109.
17. Burns A, Philpot MP, Costa DC *et al.* The Investigation of Alzheimer's Disease with Single Photon Emission Computed Tomography. J. Neurol. Neurosurg. Psych. 1989; 52: 248-253.
18. Jacobson, HG. Positron Emission Tomography - A New Approach to Brain Chemistry. JAMA 1988; 260: 2704-2710.
19. Foster NL, Chase TN, Fedio P *et al.* Alzheimer' Disease: Focal Cortical Changes Shown by PET. Neurology 1983; 33: 961-965.
20. Neary D, Snowden JS, Northen B *et al.* Dementia of the Frontal Lobe Type. J. Neurol. Neurosurg. Psych. 1988; 51: 353-361.
21. Chawluk JB, Alavi A *et al.* PET in Aging and Dementia: Effect of Cerebral Atrophy. J. Nucl. Med. 1987; 28: 431-437.
22. Estol C, Caplan LR. Therapy of Acute Stroke. Clin. Neuropharm. 1990; 13: 91-120.
23. Munoz-Garcia D, Ludwin SK. Classic and Generalized Variants of Pick's Disease: A Clinicopathological, Ultrastructural, and Immunocytochemical Comparative Study. Ann. Neurol. 1984; 16: 467-480.
24. Nagel JS, Johnson KA, Ichise M, *et al.* Decreased Iodine-123 IMP Caudate Nucleus Uptake in Patients with Huntington's Disease. Clin. Nucl. Med .1988; 13: 486-490.
25. Jagust WJ, Friedland, RP, Budinger TF. PET with FDG Differentiates Normal Pressure Hydrocephalus from Alzheimer type Dementia. J. Neurol. Neurosurg. Psych. 1985; 48: 1091-1096.
26. DeKosky ST, Shih WJ, Schmitt FA *et al.* Assessing the Utility of SPECT Scan in Alzheimer Disease: Correlation with Cognitive Severity. Alzheimer Disease & Associated Disorders 1990; 4: 14-23.
27. Montaldi D, Brooks DN, McColl JH *et al.* Measurements of rCBF and Cognitive Performance in Alzheimer's Disease. J. Neurol. Neurosurg. Psych. 1990; 53: 33-38.
28. Osimani A, Ichise M, Chung DG *et al.* Unpublished data.

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# Bone Metastasis: Radiotherapy for Effective Palliation of Pain

*Christopher C. Leighton, 9T2 and Colvin D. Springer, M.B., F.R.C.P. (C)**

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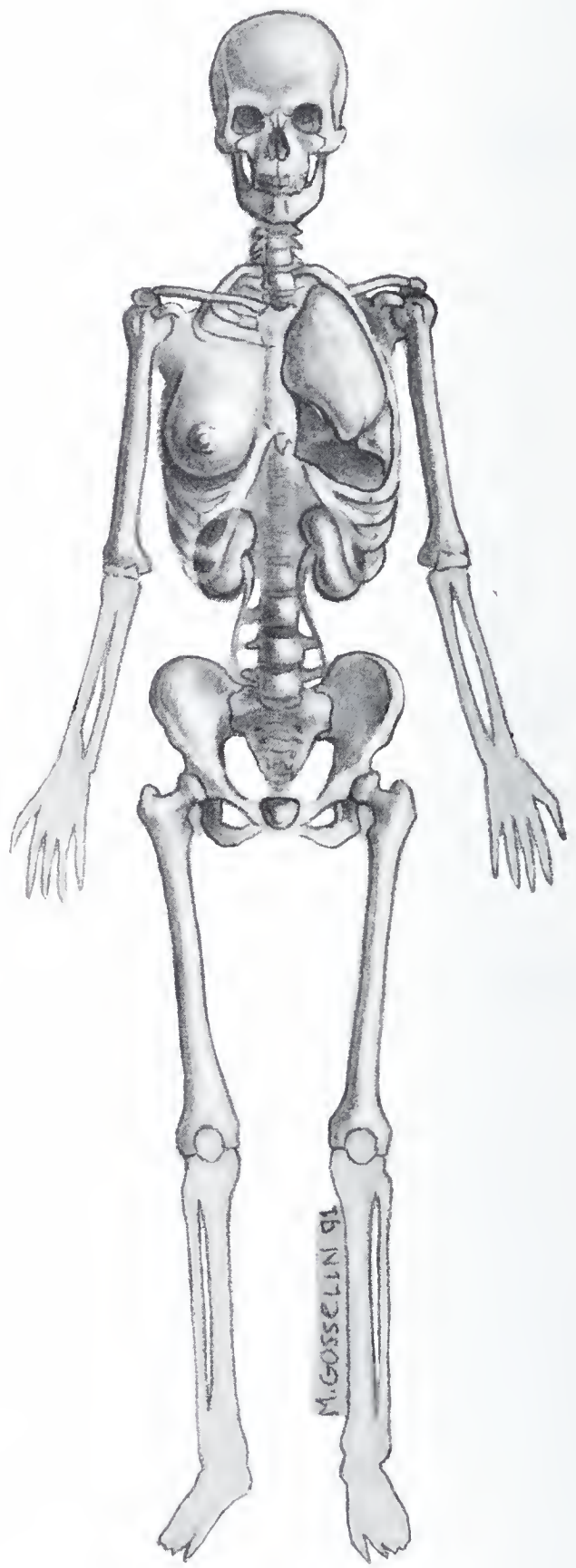
ABSTRACT

**Bone metastasis is a frequent complication of advanced malignant disease. Pain associated with bone metastasis is often severe and debilitating. Therapy for pain is palliative, and involves the use of radiotherapy. The pathophysiology and management of bone metastasis and the use of radiotherapy for palliation of symptomatic lesions is discussed. It is of current interest to use subjective patient-oriented questionnaires in the assessment of pain relief and quality of life in cancer patients receiving therapy. A preliminary study of 10 cancer patients with bone metastasis was carried out using the Short-Form McGill Pain Questionnaire and numerous quality of life measures. The McGill Pain descriptors which showed the greatest percentage decline in intensity included "Shooting", "Tender", and "Punishing-Cruel". The results imply that substantial pain control was achieved with radiotherapy, while quality of life remained at a pre-treatment level.**

ABSTRAIT

**Fréquemment, les métastases osseuses sont des complications des maladies malignes avancées. La douleur qui résulte de ces métastases est souvent très grave et débilitante. Le traitement donné est palliatif et requiert l'utilisation de la radiothérapie. La physiopathologie et les plans de traitement des métastases osseuses sont discutés. Il est de pratique courante d'employer un questionnaire subjectif axé sur le patient afin d'évaluer le soulagement de la douleur et la qualité de vie des patients qui reçoivent de la radiothérapie. Une étude préliminaire de 10 patients avec des métastases osseuses fut conduite utilisant un bref questionnaire conçu par l'université de McGill et plusieurs mesures de qualité de vie. Les résultats indiquent qu'un soulagement de douleur considérable fut attteint la radiothérapie tout en maintenant une qualité de vie à un niveau équivalent à celui avant le traitement.**




## *INTRODUCTION*

Bone metastases are a frequent manifestation in patients with advanced malignancy. In fact, they are second only to pulmonary metastases in incidence[1]. It is also known that bone metastasis is a major cause of cancer-related pain. A study of cancer patients at the Memorial Sloan-Kettering Cancer Center indicated one half of the patients reporting pain had osseous metastases as the primary cause[2]. Analgesia with NSAIDs or narcotics are usually ineffective in controlling this acute type of cancer pain. While other therapies are often prescribed, such as chemotherapy or hormonal manipulations, they usually provide pain relief for only a short time. Alternative therapy is then required; for bone metastasis this primarily involves the use of radiotherapy.

*Figure 1. Technetium bone scan of a patient with multiple widespread bone metastases from a carcinoma of the prostate. (Courtesy of Dr. I. Boxen, The Princess Margaret Hospital, Toronto, Ontario.)*

The evaluation of a radiotherapeutic treatment response in a palliative care setting is often associated with difficulty. Previously, treatment success was evaluated with outcome variables such as "complete" or "partial" pain relief[3,4]. These criteria are obviously deficient. Few have addressed the notion that pain has a major subjective component. Also, of interest is the patient's quality of life—that subjective sense of well-being. It is hoped new and more effective therapeutic regimens will arise from a better understanding of the patient's experience with disease and treatment.

## *BONE METASTASIS*

The incidence of bone metastasis is highest among four patient groups—those with primary tumours arising from the breast, prostate, lung, and kidney. These individuals account for more than 80% of those who develop bone metastases[5,6]. Metastatic bone disease is usually confined to bones containing red marrow. These include the axial skeleton as well as the ribs, proximal femora and humeri, pelvis, and calvarium. It is rare to develop bone metastases distal to the elbow or knee joints[1,5].

The pathophysiologic process which allows for bone metastasis is well documented. Vessels of the hematopoetic marrow divide into an extensive fenestrated sinusoidal system. These features allow the transport of hemopoetic cells into the blood. During muscular activity, reflux of the blood occurs through these gaps making the marrow more vulnerable to circulating malignant cells. Also, an extensive venous plexus surrounds the vertebral column and is in direct communication with the proximal lower extremities via the inferior vena cava and with the proximal upper extremeties through the superior vena cava. This venous network is in direct communication with the prostatic venous plexus inferiorly. Of significance is the consideration that this communicating venous network is valveless. Consequently, as pressure is increased in the thorax and abdomen, as in respiration, blood can flow from the vena cava through the venous plexus and enter the sinusoidal system of the axial or appendicular skeleton without entering the systemic circulation. This allows for bone metastasis without parenchymal involvement and is thought to be the mechanism of metastasis in breast, kidney, and prostatic malignancies. Contrasting this, colon cancers are drained by the portal circulation, thus making liver and lung metastases more prevalent than bone[1,5].

Pain is a major clinical consequence of osseous metastases. Characteristically, the pain is more severe at night and is pronounced by percussion over the involved bone[1]. It is thought to be the result of a number of processes: i) direct cortical bone destruction, ii) stretching of the periosteum, and iii) local release of pain sensitizers, such as prostaglandins and bradykinins[1,6,7]. Uncontrolled osseous growth of a malignancy can result in number of syndromes such as pathologic fracture, spinal cord compression, and radicular thoracic and lumbar pain[3,7]. It is therefore of clinical importance to control metastatic bone lesions, preventing such complications.

Diagnosis of bone metastasis is usually made following the development of bone pain in a patient with a history of malignancy. While the clinical history of such pain, as discussed, is often suggestive of metastasis, definitive diagnosis is made with a Technetium bone scan. "Hot spots" or areas of increased bone activity are usually seen in the patient with metastatic disease (see Figure 1). However, these are very nonspecific; the patient with active arthritis may show similar activity in regions of the affected joints. Other tests available to help support a diagnosis of bone metastasis include skeletal films, which may show sclerotic or osteolytic lesions; and the serum calcium and alkaline phosphatase which are often elevated in the presence of osseous metastases. However, osseous disease cannot be ruled out should the serum calcium and alkaline phosphatase remain within normal limits.

Therapy for bone metastasis is multimodal. Early asymptomatic disease tends to be managed with chemotherapy and hormonal manipulation where indicated. Breast and prostate malignancies may be treated with antiestrogens or antiandrogens respectively. Orchiectomy is usually performed in males with prostatic carcinoma who have demonstrated bony disease. While

**Table 1: Mean Intensity Scores of Pain Descriptors**

| Pain Descriptor | Mean Intensity Range (range 0-5) Pre-treatment (SD) | Post-treatment (SD) | % Change |
|---|---|---|---|
| 1. Throbbing | 0.6 (0.7) | 0.5 (0.8) | 17 |
| 2. Shooting | 0.7 (0.9) | 0.1 (0.3) | 86 |
| 3. Stabbing | 0.6 (0.9) | 0.5 (1.1) | 17 |
| 4. Sharp | 0.8 (1.1) | 0.6 (1.1) | 25 |
| 5. Cramping | 0.7 (1.0) | 1.0 (0.9) | 43* |
| 6. Gnawing | 1.4 (1.0) | 0.9 (0.8) | 36 |
| 7. Hot-burning | 0.7 (0.9) | 0.4 (0.7) | 43 |
| 8. Aching | 1.4 (0.7) | 1.4 (0.9) | 0 |
| 9. Heavy | 1.0 (1.1) | 0.6 (0.9) | 40 |
| 10. Tender | 1.1 (0.9) | 0.4 (0.5) | 64 |
| 11. Splitting | 0.5 (1.0) | 0.2 (0.4) | 60 |
| 12. Exhausting | 1.5 (1.0) | 1.2 (0.7) | 20 |
| 13. Sickening | 0.6 (0.9) | 0.7 (1.0) | 14* |
| 14. Fearful | 0.5 (1.0) | 0.6 (1.0) | 17* |
| 15. Punishing-cruel | 0.7 (1.2) | 0.1 (0.3) | 86 |

**denotes the worsening of the symptoms with treatment*

**Table 2**
**Mean Scores for the Sensory (S), Affective (A), Total (T), Visual Analogue Scale (VAS) and Present Pain Intensity (PPI) Scales**

| *Before R.T.* | S | A | T | VAS | PPI | ME |
|---|---|---|---|---|---|---|
| **Mean:** | 9.4 | 3.3 | 12.7 | 37 | 1.8 | 2.4 |
| **(S.D.)** | (5.6) | (3.3) | (8.3) | (27) | (1.1) | (3.9) |
| ***After R.T.*** | | | | | | |
| **Mean:** | 6.6 | 2.6 | 9.2 | 31 | 1.3 | 2.1 |
| **(S.D.)** | (4.6) | (2.4) | (6.4) | (23) | (0.6) | (3.8) |

*A narcotic score is included, expressed as a 24 h morphine equivalent dosage factor (ME) i.e. 1-10 mg i.m. morphine; R.T. – radiotherapy*

these therapies are often effective in causing the regression of osseous lesions in a majority of patients, this result is usually short-lived. Most patients will eventually develop symptoms from bony lesions. Radiotherapy then becomes important in the palliation of painful, debilitating metastases. Generally, radiotherapy is administered with a Cobalt-60 beam for treatment of symptomatic bone metastases. A standard regimen would consist of 400 cGy per day given over 5 consecutive days for a total dose of 2000 cGy (1 cGy = 1 rad). Side effects for this short course of treatment are mild and are site-specific. Pelvic irradiation may cause nausea, vomiting, and diarrhea during the treatment period. However, these symptoms usually resolve once therapy has ended.

The success of radiotherapy in relieving pain from bone metastases is well known. A compilation of five studies from 1977-82 comprising 1057 patients with over 1000 treatment sites indicated that between 73-100% of patients received some level of pain relief[2-4,8,9]. In fact, three of the five studies showed response rates at or in excess of 90%. The importance of palliative radiotherapy is also underscored by this research: One study revealed more than 50% of the patients with breast or head and neck cancer and bone metastases lived for more than one year after treatment[2]. Indeed, these patients can continue to be ambulatory for considerable time with appropriate management.

The most comprehensive work done in the evaluation of radiotherapy for bone metastases was completed by the Radiation Therapy Oncology Group (RTOG) in 1982[4]. It was identified that important prognostic indicators for favourable treatment response included the site of the primary lesion and a low initial pain score, and that the site of metastasis had no significant role in determining the likelihood or magnitude of response. In addition, it was also concluded a shorter course of radiotherapy (over one to two weeks) was as effective as a more protracted regimen. This was later disputed with a re-analysis of the data, however little additional study has centered on this concern[10]. A one to two week regimen is generally prescribed for palliation of bone metastasis.

## *PAIN ASSESSMENT*

New pain from bone metastasis represents a real crisis for the patient with malignant disease. This acute type of cancer pain not only reminds the patient of the disease, with the indication of recurrence, but it also exacerbates a fear of impending death[11]. The effect this situation has on the patient's perception of pain remains in question. It is nearly impossible to separate the influence of one's anxiety, fear, or depression from the perception of pain[12].

Difficulty arises in pain assessment when it is realized a subjective experience must be measured introspectively, and then verbally communicated to the physician[13]. Melzack's McGill Pain Questionnaire was devised to bridge this barrier[14]. The original long form (LF-MPQ) is based on sensory, affective, and evaluative word descriptors which are used by patients to specify their subjective pain experiences. A meta-analysis of 51 studies using the pain questionnaire supported its validity as a measure of pain quality and intensity[15].

Melzack devised a more abbreviated form of the MPQ: the Short Form-McGill Pain Questionnaire (SF-MPQ)[16]. It was shown to be comparable to the long form with correlations between the two being consistently high and significant[17]. It consists of 15 pain descriptors which are rated for intensity: Throbbing, Shooting, Stabbing, Sharp, Cramping, Gnawing, Hot-Burning, Aching, Heavy, Tender, Splitting, Fearful, Tiring-Exhausting, Punishing-Cruel, Sickening. In the meta-analysis these descriptors were often chosen by cancer patients to describe their pain[15]. Descriptor rankings are summarized into three scores:

sensory, affective, and total. Also included in the SF-MPQ is the present pain intensity index (PPI) as well as a visual analogue scale[13, 17, 18].

## *QUALITY OF LIFE ASSESSMENT*

Quality of life is rarely reported as an outcome measure in randomized control trials of cancer patients. Most reports focus on survival rates and rates of recurrence, ignoring the subjective experience of the cancer patient who must endure various toxic treatment regimens. Despite their infrequent use, there are a number of accurate quality of life measures which are feasible to use in a clinical setting[19-22].

In a recent review of quality of life scales, Donovan et al. stressed a quality of life measure should be able to measure changes following disease progression[20]. Three characteristics were identified as central to this detection: i) Include enough items per scale, ii) include a range of response alternatives such as "strongly agree" to "strongly disagree", and iii) include domain scores, as well as a single scale summary score.

## *EFFICACY OF RADIOTHERAPY*

A preliminary review of 10 cancer patients receiving radiotherapy for bone metastasis was made at the Windsor Regional Cancer Center. Patients were chosen according to a set of inclusion criteria. Most important was the provision that the study was done on ambulatory patients receiving radiotherapy for bone metastasis for the first time. Assessments were made on the first and last days of one to two week regimen of radiotherapy. The Short-Form McGill Pain Questionnaire, a number of quality of life scales, and a medication inventory were completed with each assessment.

## *RESULTS*

The mean scores of the pain descriptors of the Short-Form McGill Pain Questionnaire (SF-MPQ) are included in Table 1. Intensity rankings decreased in 11 of the 15 descriptors. The greatest percentage of decline in intensity was seen in the rankings of the descriptors "Shooting", "Punishing-Cruel" and "Tender", supporting the premise that radiotherapy is effective in alleviating intense bone pain. Comprehensive scores from the SF-MPQ including the Sensory, Affective, and Total scores, as well as the Visual Analogue Scale, and the Present Pain Intensity were determined. A narcotic score was also assigned before and after therapy. The means and standard deviations of these values are included in Table 2. All showed a decline indicating pain control was improved with radiotherapy. Due to the small patient sample, statistical significance was not assessed. These summary scores are most important in relating the response to therapy. The individual descriptors are more focused on a particular sensation; and any one descriptor may not show a change.

Quality of life measures showed little or no change over the course of therapy. Nausea, vomiting, diarrhea, and appetite were worsened by the end of radiotherapy. There were no significant skin reactions.

## *CONCLUSIONS*

Bone metastasis represents a serious complication in the patient with malignant disease. Management should center on providing as much pain relief as possible. Radiotherapy is indicated when pain from metastases is no longer relieved with narcotics or in such cases where progression of the lesion would be grave, as in spinal cord compression. Patient-centered subjective questionnaires, such as the Short-Form McGill Pain Questionnaire, are a valuable means of fully assessing the patient with symptomatic bone metastases.

## *REFERENCES*


1. Hendrickson FR, Sheinkop MB. Management of osseous metastases. Sem. Oncol. 1975; 2: 399-404.
2. Vikram B, Chu FCH. Radiation therapy for metastases to the base of the skull. Radiology 1979; 130: 465-468.
3. Cheng DS, Seitz CB, Eyre HJ. Nonoperative management of femoral, humeral, and acetabular metastases in patients with breast carcinoma. Cancer 1980; 45: 1533-1537.
4. Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases. Final results of the study by the Radiation Therapy Oncology Group. Cancer 1982; 50: 893-899.
5. Mirra JM. Metastases. In: Bone Tumors: Clinical, radiologic and pathologic correlations. Vol 2, Lea and Febeger, Philadelphia PA, USA
1989; 1496-1516.
6. Kinsella TJ. Radiation therapy for metastatic disease. In: Oncologic Therapeutics 1989/1990. RE Wittes (Ed.), JB Lippincott Co., Philadelphia PA, USA 1989; 432-433.
7. Yarnold JR. Role of radiotherapy in the management of metastases from breast cancer. J. Royal Soc. Med. Suppl. 1985; 78: 23-25.
8. Gilbert HA, Kagan AR. Evaluation of radiation therapy for bone metastases: Pain relief and quality of life. Am. J. Roentgenol. 1977; 129: 1095-1096.
9. Garmatais CJ, Chu FCH. The effectiveness of radiation therapy in the treatment of bone metastases from breast cancer. Radiology 1978; 126: 235-237.
10. Blitzer PH. Reanalysis of the RTOG study of the palliation of symptomatic osseous metastases. Cancer 1985; 55: 1468-1472.
11. Foley KM. The treatment of cancer pain. New Eng J. Med. 1985; 313: 84-93.
12. Cleeland CS. The impact of pain on the patient with cancer. Cancer 1980; 45: 1533-1537.
13. Houde RW. Methods for measuring clinical pain in humans. Acta Anaesth. Scand. 1982; 74: 25-29.
14. Melzack R. The McGill Pain Questionnaire: Major properties and scoring methods. Pain 1975; 5: 277-299.
15. Wilke DJ, Savedra MC, Holzemer WL, Tesler MD, Paul SM. Use of the McGill Pain Questionnaire to measure pain: A meta-analysis. Nursing Res. 1990; 39: 36-40.
16. Melzack R. The short-form McGill Pain Questionnaire: Major properties and scoring methods. Pain 1987; 30; 191-197.
17. Scott J, Huskisson EC. Graphic representation of pain. Pain 1976; 2; 175-184.
18. Huskisson EC. Measurement of pain. Lancet 1974; 2: 1127-1131.
19. Selby PJ, Chapman JA, Etazadi-Amoli J, Dalley D, Boyd NF. The development of a method for assessing the quality of life of cancer patients. Br. J. Cancer 1984; 50: 13-22.
20. Donovan K, Sanson-Fisher RW, Redman S. Measuring quality of life in cancer patients. J. Clin Oncol. 1989; 7: 959-968.
21. Guyatt GH, Veldhuyzen Van Zanten SJ, Feeny DH, Patrick DL. Measuring quality of life in clinical trials: A taxonomy review. CMAJ, 1989; 140: 645-650.
22. Schipper H, Clinch J, McMurray A, Levitt M. Measuring the quality of life of cancer patients: The functional living index-cancer: Development and validation. J. Clin. Oncol. 1984; 2: 472-483.

# The Principles of Osteochondral Allografts

*Mohammed N. Mahomed, 9T2*

ABSTRACT

**The concept of allograft bone transplantation began at the turn of this century when Lexer first reported his findings on the subject. Since then, data on the use of fresh and frozen allografts in orthopaedic surgery have accumulated over the years. During the early part of the last decade, the popularity of allografts and bone banks decreased due to the fear of transmissible diseases such as hepatitis and AIDS. Recent results regarding the long term effectiveness of allografts combined with data which places the risk of disease transmission to be less than previously speculated, have caused a resurgence of interest in this field. This article will review the principles involved in operating a bone bank and the use of allografts in orthopaedic surgery.**

ABSTRAIT

**Le concept de la transplantation d'os allogreffes a commencé au début du siècle lorsque Lexer a rapporté pour la première fois ses découvertes sur ce sujet. Depuis ce temps, des donneés sur l'utilisation des allogreffes frais et congêlés en chirurgie orthopédique se sont accumulées. Au début de la dernière décenie, la popularité des allogreffes et des banques d'os a diminué due aux craintes des maladies transmissibles comme l'hépatite et le SIDA. Des nouveaux résultats concernant l'éfficacité à long terme de l'utilisation des allogreffes ont été publiés. Ces résultats ainsi que des données qui calculent le risque de transmission des maladies á un taux moins élévé qu'on le pensait auparavant ont causé un nouveau surgissement d'intérêt dans ce domaine. Cette article révise les principes impliquées dans l'opération dans l'opération d'une banque d'os dans l'utilisation des allogreffes en chirurgie orthopédique.**

## *INTRODUCTION*

The use of bone allografts in orthopaedic surgery dates back to 1908 when Lexer first published his results[1,2]. Since then, interest in the use of bone allografts has steadily increased over the years. Initial success in their use was limited to limb salvage in cases of severe trauma such as from war injuries. With time, techniques and knowledge regarding bone grafting improved and the applications of bone allografts increased.

In the 1960's and 1970's the popularity of artificial hip and knee implants increased in the surgical community. Results demonstrated that cemented hip prostheses gave a ten year lifespan of useful function to the patient. This served well for the elderly patient with low demand. The problems however, arose in those patients who survived the lifespan of the implant and required replacement prostheses.

In revising cemented components, a portion of the patient's own bone stock was unavoidably lost in removing the prosthesis. This presented a problem in revision surgery, especially during the third, fourth, or later revisions as there may have been insufficient bone to achieve adequate fixation of the prosthesis[3,4]. As it became necessary to restore bone stock in order to insert a new implant it was discovered that allograft bone could be used for this.

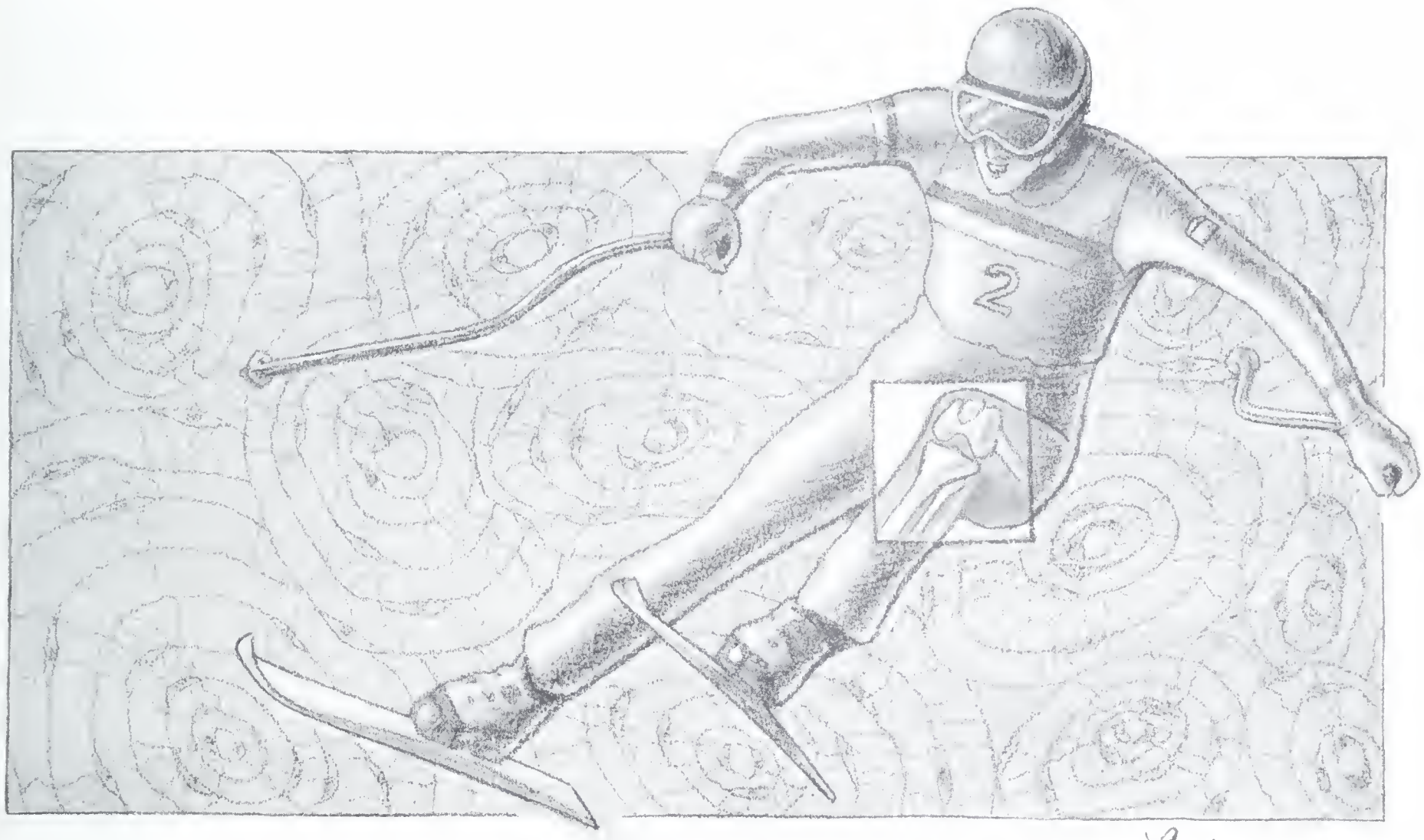
During the same time period, advances were made in the diagnosis and chemotherapeutic treatment of bone tumours. These advances made it possible to perform limb salvage surgery rather than amputation in patients afflicted with such tumours. Large defects created by en bloc resection of bone tumours would require reconstruction with either large implants, allografts, or combinations of implants and allografts (bioimplants). When allografts were used by themselves, they were either segmental (bone only) to reconstruct a defect not involving a joint, or osteochondral (bone and cartilage) where the joint was involved. The segmental grafts were frozen while the osteochondral grafts were either frozen or fresh depending on the urgency of the situation. Recently there has been more emphasis on a combination of implant and allograft, particularly for the hip. An artificial articulation supported by allograft is used for the reconstruction.

Another use of allograft bone is the correction of traumatic bone and cartilage deficits in articulating joints. In this application, fresh allografts are used because of their increased potential for cartilage viability. The use of allografts is more advantageous than joint replacement in young, active patients since increased demand on the joint in young patients limits the efficiency of artificial knees. The allograft provides a grace period of several years wherein the patient can avoid having an implant requiring frequent revision.

The effectiveness of allograft bone to replace lost bone stock in tumours, revision arthroplasties, and traumatic defects created a surge of interest in this field. This enthusiasm resulted in the establishment of numerous bone banks around the globe.

During the late seventies and early eighties, fears began to surface about the transmission of infectious agents such as the Hepatitis B and C viruses and the Human Immunodeficiency virus through various body substances. Many transplant centres either closed down or markedly curtailed their bone bank programmes because of this fear. Physicians viewed such procedures as non-life saving and felt that the possible risk of infecting patients outweighed the benefits. At this time, testing for HIV was not possible and very little was known about the disease, its transmission, and incidence.

Presently, the use of osteochondral allografts is again on the rise. This resurgence of interest is due to recent research on the




long term effectiveness of the allografts and the actual risk of disease transmission. Recently, it has been estimated that the risk of transmission of the HIV virus in banked bone is approximately 1 in 1,250,000 in a properly screened programme[5]. This figure is much lower than was previously believed. As well, studies evaluating the long term effectiveness of allografts in joints such as the knee have shown a mean survival time of seven years[6]. This survival time is extremely important in cases of traumatic defects that need repair in young, high demand patients. With such low risks and proven long term effectiveness, the number of patients being treated with bone allografts is rapidly increasing.

The Bone Bank Programme at the University of Toronto started in 1971 and is one of the largest programmes of its kind in the world. The programme is comprised of four major components: 1. Deep frozen allograft bone which is used in general orthopaedic procedures such as grafting bone cavities. 2. Fresh small fragment osteochondral allografts which are used for articular surface replacement of traumatic defects. 3. Deep frozen allograft bone which is used for bone stock replacement in revision arthroplasty surgery. 4. Deep frozen large fragment allograft bone for limb salvage after en bloc excision of bone tumours. Clinical and research experience over the past 18 years have shown that the above mentioned uses of fresh and frozen allograft bones are successful in the treatment of the conditions listed.

## *BONE BANKING PROCEDURE*

Currently at the Mount Sinai Hospital Transplant programme, the protocol for bone allograft transplantation is very stringent and thorough. In order for a donor to be accepted into the programme, he/she must be between the ages of 18 and 60 if the tissues are to be used as frozen allografts and 18 to 30 if they are to be used as fresh allografts. The bone should be harvested within 12 hours after death if the cadaver is kept at room temperature or within 24 hours after death if stored in refrigeration (8 degrees Celsius or less). The donor's medical history is always reviewed. If any of the criteria listed in Table I are present, the donor is then rejected from the programme[7].

The acceptable bone is then harvested in an operating room under sterile conditions. Each bone is swabbed and cultured and blood samples are taken in order to test for various conditions. The fresh grafts are immersed in a sterile container at 4°C containing: one liter Ringer's lactate solution, one gram Cefazolin (Ancef), and 50,000 units Bacitracin (usually three liters are required per knee joint). The grafts are wrapped in multiple layers of sterile plastic and rapidly transported to the central freezing facility at the Mount Sinai Hospital.

The newly harvested bone is stored in a separate freezer at minus 20°C until the laboratory tests are back from the donor's tissues. Various tests conducted on the tissues include a hepatitis

**Table 1: Criteria for Rejection of Donor Allograft**

| | |
|---|---|
| 1. | Active systemic infection. |
| 2. | Active [illegible] involving the tissue to be procured. |
| 3. | A [illegible] history of a slow viral disease. |
| 4. | Malignancy with possible exception of primary non-[illegible] CNS tumours. |
| 5. | [illegible] or existence of active hepatitis, or unexplained jaundice. |
| 6. | History of HIV positive blood or high risk individuals (homosexuals, haemophiliacs, or immigrants from countries of endemic HIV: Central Africa and Haiti). |
| 7. | Diffuse connective tissue diseases, metabolic bone diseases, and other serious systemic disorders of unknown etiology. |
| 8. | Death from unknown causes. |
| 9. | Chronic parenteral drug abuse. |
| 10. | Toxic substances which may be transferred in toxic doses. |

screen, a HIV test by Elisa, and a VDRL in addition to serology and cultures. If all tests are negative, the bone is then irradiated with 2.5 M rads of gamma radiation. This dose is bactericidal, viricidal, and is a true sterilization procedure which kills the most radioresistant organisms known to man, Bacillus Niger Spores, without rendering the bone radioactive. The frozen grafts are then transferred to the main freezer and stored at -70° C until they are used. The fresh grafts are usually transplanted into recipients within 24 hours of removal from the donor. The combination of donor screening, tissue testing, and bone irradiation make the risk of transmitting infectious agents almost negligible.

## *FRESH VERSUS FROZEN ALLOGRAFTS*

The indications for fresh as compared to frozen allografts are based on the types of tissue involved. Studies have shown that cryopreservation damages the chondrocytes and severely diminishes the viability of articular cartilage in allograft transplantation. The intact articular cartilage, where no chondrocyte exposure occurs, is immunoprotected and shows no detectable cell mediated or humoral response from the host. For this reason the use of fresh cartilage is no more immunogenic than frozen cartilage in human beings. In the case of osseous tissue, cryopreservation has no significant effect on the viability of cells since in both fresh or frozen states, the cells are nonviable. Langer and associates have shown that there is only a small difference in the antigenicity of fresh versus frozen allograft bone[8,9].

In applications where articular cartilage is needed, such as for traumatic defects of the knee, fresh allografts are used since the potential viability of the cartilage is greatly enhanced while the immunogenicity of the bone does not significantly differ from the use of frozen grafts. In applications where only bone is transplanted, the convenience of storage and availability make the use of frozen grafts more favourable by allowing for elective surgery instead of urgent surgery.

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## *INDICATIONS FOR ALLOGRAFTING*

Initially, allograft bone was used to treat bony abnormalities due to a wide array of etiologies. Conditions such as trauma, osteoarthritis, osteonecrosis, and osteochondritis dissecans were all treated by allografts. Research over the past twenty years has shown that some of these etiologies are better suited than others for the application of osteochondral allografts. In a review of the first 90 cases of fresh osteochondral allografts of the knee, McDermott has shown that defects of the knee caused by trauma do much better in long term follow up as compared to defects caused by either osteoarthritis or osteonecrosis (Table 2). As a result, current recommendations for the use of fresh osteochondral allografts are for the repair of defects of articulating joints such as the knee due to trauma and possibly osteonecrosis[10,11].

**Table 2: Etiology and Success of Osteochondral Allografts of the Knee**

| Etiology | No. of Patients | Percent Success |
|---|---|---|
| **Trauma:** | | |
| Tibial Plateau | 36 | 69 |
| Femoral Condyle | 12 | 91 |
| Osteoarthritis | 24 | 42 |
| Osteochondritis Dissecans | 4 | 25 |
| **Osteonecrosis** | | |
| Spontaneous (SONK) | 11 | 27 |
| Steroids | 3 | 0 |
| **Total** | 90 | 56 |

In the application of bony deficit replacement from tumour surgery, the type of graft used depends on the type of procedure to be performed. When limb salvage procedures are being performed, the type of graft depends on the site, extent, and nature of the tumour. In slow growing tumours involving a joint, the surgical team waits for an appropriate donor to become available and then a large fragment fresh osteochondral allograft is performed. This type of graft includes both bone and cartilage, which has a higher potential viability in fresh grafts. In rapidly growing tumours of an articulating joint where waiting may reduce the survival rate, there are two possible types of surgery for palliation. In order for the patient to be able to remain mobile one can use either a frozen, large fragment allograft alone, or a combination of allograft and prosthesis specially designed for tumour patients. In cases where the tumour involves only a segment of bone not involved in articulation, a large fragment frozen allograft can provide good structural support as well as providing the convenience of elective surgery[12,13].

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Allografts are also used frequently in surgery for the revision of artificial joints as frozen allograft bone has similar mechanical properties to live bone. The allograft bone is used in both the acetabular side and the femoral side of the hip joint. In the acetabulum, morcellized or sliced male femoral heads can be used along with acetabular prosthetic cups to restore protrusion defects in the medial wall of the wall. Femoral head slices may also be used for shelf reconstruction of superio-lateral acetabular wall deficiencies. For cases of large pelvic defects involving the anterior and/or posterior columns and/or the dome of the acetabulum, partial or complete frozen allograft acetabulae can be used and provide excellent results.

On the femoral side of the hip joint, proximal femoral deficits can be replaced by either allograft femurs or tibial allografts which are cemented to the prosthesis but not to the host bone. In order to achieve good results, the graft should be longer than two cm in the medial longitudinal axis and have no holes drilled in it. A general principle in revision allografting is that the allograft-host bone interface should not be cemented. This is to allow for integration of host bone into the allograft; a process that takes approximately 14 months. During this time, it is important to ensure adequate fixation of the graft in order for integration to occur[14].

A new function of bone banks is their role in sports medicine. Some banks are now collecting menisci, ligaments, and tendons in addition to bone. The menisci are used to replace damaged menisci in the knee[15]. The ligaments and tendons are used for the reconstruction of cruciate ligaments. Ligaments and tendons provide a more natural replacement for torn cruciates, especially in light of poor results attained with the use of synthetic gortex replacements.

## *DISCUSSION*

The procedure of osteochondral allografting is effective in dealing with loss of bone and/or cartilage in patients. The type of graft to be used determines whether or not cryopreservation is required. The act of cryopreservation itself does not significantly alter the antigenicity of the bone and thus does not affect the outcome of the procedure. In instances where a joint surface requires replacement, the advantage of potential fresh chondrocyte viability deems that the graft not be frozen but rather transplanted within 24 hours of procurement. In the matching of graft to recipient, blood typing or HLA matching is not necessary. Studies have shown that the graft bone, which is mainly matrix and minerals, does not induce a significant host response. Similarly the cartilage has a protective matrix about the cells which is also non-immunogenic. If bone without cartilage is being transplanted, the deep frozen preserved tissue is comparable to fresh tissue and allows the surgery to be performed electively.

With the proper management of a bone bank, including the screening of donors, testing of tissues, the use of sterile techniques, and irradiation of grafts, the risk of transmitting infectious agents is extremely low. In addition, because the bone itself does not incite a significant host response, the need for immunosuppression in allograft recipients is unnecessary. This leaves the host better equipped to fight an infection in the unlikely event that he/she acquires one.

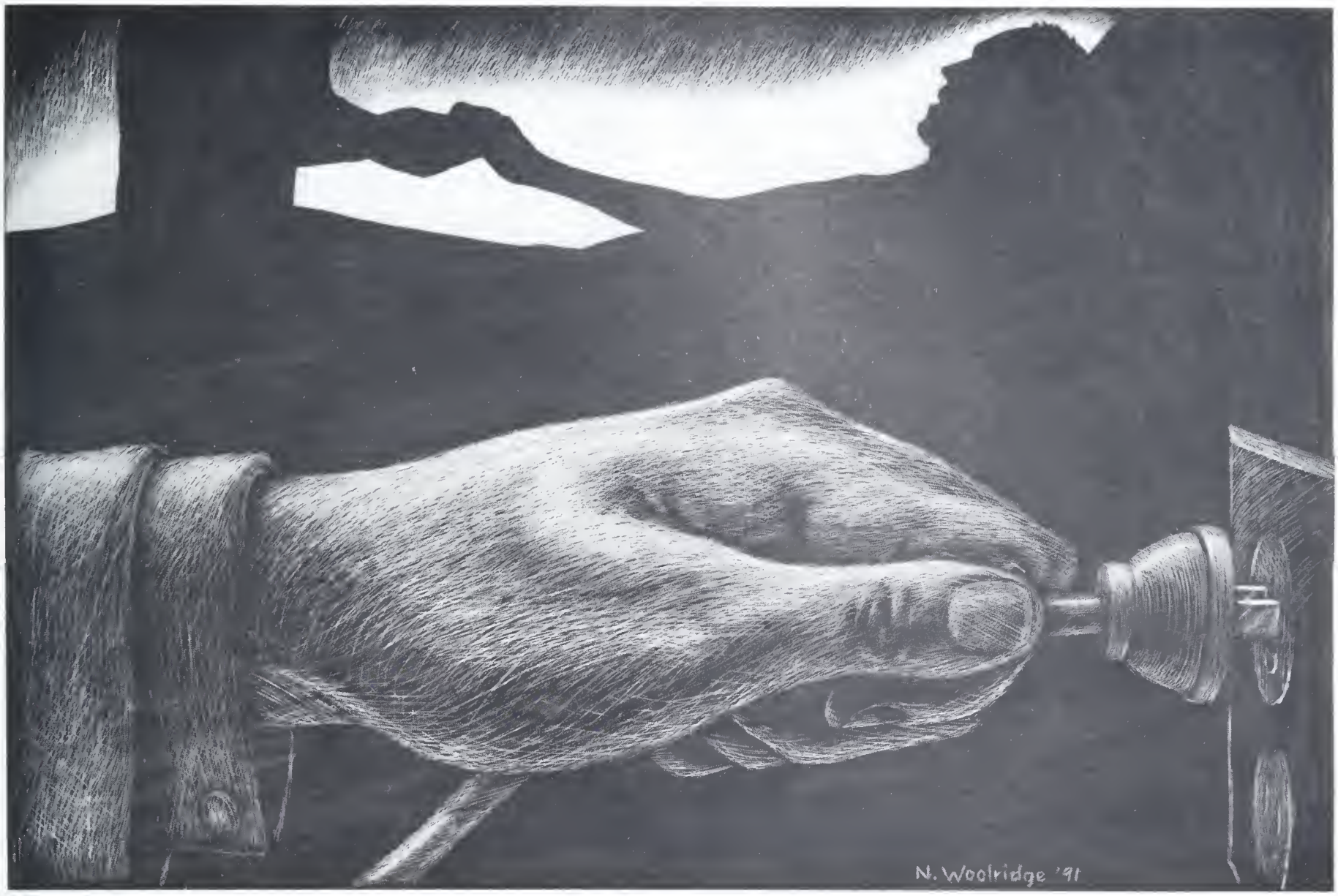
Clearly, as our experience with cemented prostheses has shown, their limited lifespan combined with the loss of bone stock during revision makes the use of allograft bone a useful adjunct to treatment. In addition, in cases of traumatic defects in articulating joints, especially in young, high demand patients, allografts provide a much better alternative to total joint replacements which have not been effective in these patients. Thus the use of allografts in orthopaedics is a rapidly expanding area attracting a great deal of interest. Until a clinically useful bone substitute can be developed, the use of allografts and bone banks will increase as the number of patients requiring their use continues to grow.

## *ACKNOWLEDGEMENTS*

I would like to thank Dr. Allan E. Gross, Professor and Chairman of the Division of Orthopaedic Surgery, for his help and support in writing this paper.

## *REFERENCES*

1. Lexer E: Die Verwendung der freien Knochenplastik nebst Versuchen uber Gelenversteifung und Gelenktransplantation. Arch. Kiln. Chir. 1908; 86:939
2. Lexer E: Joint Transplantation and Arthroplasty. *Surg. Gyne. & Obs.* 1925; 40:782-809
3. Gross AE, Rudan JS, McAuley JP et al: The Use of Allografts in Orthopaedic Surgery. Curr. Orthop. 1988; 2:22-27
4. Oakeshott RD, McAuley, JP, Gross AE et al.: *Bone Transplantation: Allograft Reconstruction in Revision Total Hip Surgery*, Ed Aebi and Regazzoni, Springer-Verlag, Berlin, 1989; 265-274
5. Buck BE Malinin TI, Brown MD: Bone Transplantation and Human Immunodeficiency Virus. Clin. Orthop. 1989; 240:129-136
6. Dr. Richard J. Beaver, Personal Communication.
7. Gross AE, Langer F, McKee N et al.: A Comprehensive Orthopedic Transplant Unit. Transplantation Today 1985; 2:38-44
8. Langer F, Czitrom AA, Pritzker KPH et al: The Immunogenicity of Fresh and Frozen Allogeneic Bone. JBJS-A 1975; 2:216-220
9. Czitrom AA, Keating S, Gross AE et al: The Viability of Articular Cartilage in Fresh Osteochondral Allografts after Clinical Transplantation. JBJS-B 1990; 4:574-581
10. McDermott AGP, Langer F, Pritzker KPH et al: Fresh Small-Fragment Osteochondral Allografts -Long-term follow-up study on first 100 cases. Clin. Orthop. 1985; 197:96-102
11. Zukor DJ Paitich B, Oakeshott RD et al: *Bone Transplation: Reconstruction of [10]Post-Traumatic Articular Surface Defects Using Fresh Small-Fragment Osteochondral Allografts*, Ed Aebi and Regazzoni, Springer-Verlag, Berlin, 1989; 293-305
12. Gross AE, McKee N, Farine I et al: *Current Concepts of Diagnosis and Treatment of Bone and Soft Tissue Tumors: Reconstruction of Skeletal Defects Following En-Bloc Excision of Bone Tumors*, Springer-Verlag, Berlin, 1984; 163-174
13. Gross AE, McKee N, Langer F et al: *Osteochondral Allografts, Biology, Banking and Clinical Applications: Storage and preservation of viable articular cartilage*, Ed Friedlander GE et al. Little, Brown, Boston, 1983; 73-79
14. Dr. Gordon Allan, Personal Communication
15. Arnoczky SP, MacDewitt CA, Cuzzell JZ et al: Meniscal Replacement Using a Cryopreserved Allograft -an experimental study in dogs. *Clin. Orthop.* 1990; 252:121




# Euthanasia: On Intending Death

*Andrew Pierre, 9T3*

ABSTRACT

The Oxford Dictionary defines euthanasia as the bringing about of a gentle and easy death, especially in the case of incurable and painful disease. General approval of euthanasia has increased significantly over the past few decades. It seems that a pro-death ideology has gained strength in recent years. What factors might explain this? Perhaps the progress made in providing human comfort has made pain and suffering less tolerable and death more acceptable. Perhaps the success medicine achieves in prolonging the dying process has begun to enhance the attractiveness of a quick death. Another factor might be an emphasis on individual rights. Popular expressions like "the right to die" suggest to some people a personal right to end their life. However, peoples' attitudes toward a moral issue do not change its nature; if it is wrong it shall continue to be so regardless of people's opinions and practices. Is it morally right then for a human being to take it upon himself to choose the moment and mode of death, attempting to make it as painless and dignified as possible? Such is the question at the hear of the euthanasia debate.

ABSTRAIT

D'après le dictionnaire Oxford, l'euthanasie est l'action d'abréger la vie, surtout en parlant des incurables, d'une façon tranquille et sans heurts. Durant les dernières décenies, l'assentiment du public envers l'euthanasie a augmenté considérablement. Il semble qu'une idéologie en faveur d'une telle mort a connu de la force dans ces dernières années. Comment peut-on expliqué cela? Il se peut que le confort humain qu'amène le progrès de notre société a rendu la souffrance et la douleur moins tolérable et la mort plus acceptable dans certaines circonstances. Il est aussi possible que le succès que possède la médicine d'être capable de prolonger le processus de la mort commence à rendre l'idée d'une mort rapide plus attrayante. De plus, l'emphase mit sur les droigts de l'individu pourrait être un autre facteur. Des expressions populaires comme "le droigt de mourir" suggère, à certaines gens, le droigt d'une personne de pouvoir terminer sa vie. Cependant, les attitudes du public envers une issue de moralité ne change pas la nature de celle-ci; c'est-à-dire, lorsque cette nature est injuste ou mauvaise, elle demeure ainsi qu'importe les opinions et les habitudes de la population. Alors, est-ce conforme à la morale qu'un individu soit capable de choisir par lui-même son temps et sa façon de mourir avec autant de dignité et le moins de mal que possible? C'est ainsi la question au coeur des discussions auprès de l'euthanasie.

The modern meaning of the word euthanasia is "mercy killing", or the deliberate bringing about of death for reasons of mercy. In the strict sense, one kills a person when, having considered bringing about a person's death as something one could do, one commits oneself to doing it by adopting this proposal instead of some alternative and by undertaking to execute it. By definition killing in the strict sense is an action contrary to the good of life. The adoption of a proposal to bring about someone's death is incompatible with respect for the good. Thus, every act of euthanasia, which is an act of killing in the strict sense, is immoral if one accepts that life has intrinsic value[1]. Then no additional circumstance or condition can remove this immorality. But society is faced with differing opinions on the ethical justification of euthanasia, and with especially strong sympathy for voluntary euthanasia in the face of terminal illness. Is it morally right then for a human being to intend death as a means to the relief of suffering?

Joseph Fletcher puts forward an argument for voluntary beneficent euthanasia based on the premise that life is not an intrinsic good. He is primarily concerned with human need - both of life and of death. So in the balance of biological life and human life, being a person is of more value than simply being alive. The essence of this argument is that we should not consider life an intrinsic good and should embrace a quality-of-life ethic instead.

According to Fletcher, the loss of personal integrity now often occurs long before biological death. Patients do not meet death anymore; the end comes for them while comatose, intubated, aerated, glucosed, narcosed, sedated - not conscious, not even human anymore[2].

This loss of integrity is what makes us "not even human anymore." The heart of the matter lies with dignity, the having of which roughly denotes the actual ability of a human being rationally to determine and control his or her life. For Fletcher, a person's rational faculty is the core of human being - not spontaneous organ function, but cerebral function. From his point of view, dignity has been lost, and death can be said to have ensued when cortical function is irreversibly lost.

He also asserts that humans should assume an initiative in dying, that being "the termination of subhuman life in post human beings." By "subhuman" he means life that has lost its dignity or integrity, and a being in such a position he terms "post human". He is clearly making a distinction between being human, and being alive and in some cases being conscious as well.

He continues: The rightness or wrongness of euthanasia, whether direct or indirect, depends on this distinction. It depends on the meta-ethical question: What does it mean to be human? There are two points to Fletcher's criteria of human ontogeny: i) To be human is to have the dignity and integrity which makes it possible to have a reasonable control over the major aspects of one's life and ii) To be human is to have proper cortical brain function.

Fletcher's criteria suffers from an inherent ambiguity in its formulation. Accordingly, someone who has lost reasonable control of his or her life is subhuman and a candidate for euthanasia. Secondly, a person who has lost proper cortical function is also subhuman and therefore a candidate for euthanasia as well. But it is entirely possible that someone may have lost control of his or her life and still have proper cortical brain function. Under the first point, euthanasia would be called for, but not under the second. Moreover, how can a patient request euthanasia unless he or she has proper cortical function? Thus the second point would rule out voluntary euthanasia for it takes a conscious person to express a wish to die.

Fletcher admits that life is a necessary condition or essential means for the attainment of any other human good. His point of disagreement with traditional ethical theory is the question of whether life is only a necessary condition for realizing other human goods or if it is also an integral component of human existence which should be protected and promoted on its own account. He considers life only a necessary condition for the reaction of other, specifically personal goods, suggesting that to consider it inherently good would be to absolutize it and thus to distort its proper role in one's hierarchy of values. According to his view, ethical theories which insist upon the sanctity of life defer too much to this value, so that instead of life serving the person, it becomes a dominant consideration and claims an unwarranted mastery which is offensive to personal dignity.

The proposition that life is only instrumentally good implies that the human person or some parts of the human person are one thing and that a person's living body is quite another thing. This implied position is dualism. Fletcher and many others implicitly embrace dualism. Fletcher sharply divided the person and personal goods from the body and physical nature, which he considers to be "out there" and "over against us". He asserts his dualistic view this way: "To perceive this is to grasp the error lurking in the notion - widespread in medical circles - that life as such is the highest good. This kind of vitalism seduces its victims into being more loyal to the physical spark of mere biological life than to the personality values of self-possession and human integrity. The beauty and spiritual depths of human stature are what should be conserved in our value system, with the flesh as a means rather than the end"[3].

Although Fletcher is mistaken in thinking that one who does not treat life as a merely instrumental value must regard it as the highest good, he is quite right in holding that dualism and the thesis that human life is only an instrumental good of persons are necessarily connected. In fact, the view that life is a merely instrumental good implies dualism.

But the dualism to which an instrumentalist view of life inevitably leads is false. Many have tried to hold some version of dualism, but it is an untenable position[4].

Both classical and contemporary philosophers - and among the latter Jacques Maritain, Etienne Gilson, Jean-Paul Sartre, Gabriel Marcel and Emmanuel Mournier - have pointed out the many problems of dualism[5]. If one thinks of the human individual as made up of a duality, how are the two parts to be distinguished? Where is one to draw the line between the person as end and the person as mere means? Asking where the line is to be drawn leads us to the clearer understanding that no line can be drawn.

Life is not merely one process among others, which might be distinguished from breathing, feeling pain, or talking. The life of a human person is indistinguishable from the very reality of the person; thus it follows that human persons and human beings are the same. Indeed, human persons are bodily beings. But Fletcher does not see life as a direct aspect of human persons, for if he did, the mere fact that a human body still lives would be enough to assure him that this individual is still a person.

Part of Fletcher's argument for voluntary euthanasia is that persons should be able to dispose of their lives autonomously, to avoid unnecessary pain and suffering and the indignity of slow deterioration, loss of control of themselves, and so on. But pain and loss of control befall the organism, which on a dualistic account is quite distinct from the person as end. How then, can what befalls the organism detract from personal dignity? Consistent dualists should say that their own living bodies simply have nothing to do with personal dignity. Pain and suffering, deterioration and loss of control, machinery and probings - these are indignities to the dying. But why would they be indignities if they bore upon what has dignity - the person - but only upon something instrumental: a living and dying organism which has somehow been once connected with a human person?

Therefore, since dualism is untenable, so is the instrumentalist conception of human life which implies dualism. And like consequentialism, this dualistic view underlies most pro-euthanasia arguments. But if consequentialism and the theory that human life is only an instrumental good are both admitted to be false, then the rationale of the proponents of euthanasia is almost wholly destroyed.

Below is the view articulated by the House of Delegates of the American Medical Association:

"The intentional termination of the life of one human being by another - mercy killing - is contrary to that for which the medical profession stands and is contrary to the policy of the American Medical Association.

The cessation of the employment of extra-ordinary means to prolong the life of the body when there is irrefutable evidence that biological death is imminent is the decision of the patient and/or his immediate family. The advice and judgement of the physician should be freely available to the patient and/or his immediate family"[6].

Crucial to a just interpretation of this view is what is meant by extra-ordinary means of preserving life. Paul Ramsey presents it well:

"Ordinary means of preserving life are all medicines, treatments, and operations, which offer a reasonable hope of benefit for the patient and which can be obtained and used without excessive expense, pain, and other inconveniences.

Extra-ordinary means of preserving life are all those medicines, treatments, and operation which cannot be obtained without excessive expense, pain, or other inconvenience, or which, if used, would not offer a reasonable hope of benefit"[7].

Now with this distinction in mind, I propose that the intentional termination of human life is impermissible, irrespective of whether this goal is brought about by action or inaction. If the action or omission is aimed at producing a death, then the act or omission is morally wrong. It is wrong because life is an intrinsic good, and the intent is to violate that good.

But it is entirely possible that the choice of a physician not to use extra-ordinary means for preserving life may be prompted not by an intent to bring about death, but by other motives which do not violate the good of life. The doctor who does what he or she can to comfort the patient for whom there is no ordinary means of treatment, but does not submit him or her to extra-ordinary treatment, may foresee that the decision will hasten death, but it certainly does not follow that therefore the doctor intends to bring about the death of the patient.

But the refusal to use ordinary means is an altogether different matter. After all, what is the point of refusing assistance which offers reasonable hope of benefit to the patient without involving excessive pain or other inconvenience? The refusal is motivated by a desire to bring about the death of the patient. Such philosophy therefore rules out not only direct actions to bring about death, such as giving a lethal injection, but intentional neglect as well, such as not providing minimum care for the person.

In summary, the intentional termination of life, whether by active to passive euthanasia, must be forbidden on the grounds that life is an intrinsic good. But the cessation of extra-ordinary means is morally permissible because, though death is foreseen, it need not therefore be intended.

For Ramsey[8], the practice of mercy killing of a person who requests death raises moral objections comparable to those posed by suicide. His ethical objections to both are linked to the inviolability of human life. Even when a suffering person requests to be put to death, the act of mercy killing remains a human act directly aimed at destroying the good of a human life.

Hence, the unfortunate situation of a person who wishes to be put to death does not change the moral significance of the act of killing, attacking the good of life itself. Human life is not the only good, but it remains one of the basic goods of human existence

nonetheless, and each cannot be subordinated to any of the others.

But as in the case of suicide, some, like Fletcher, wish to admit of reasons which may outweigh the evil of taking human life. Their position rests on an analysis of human acts in which acting against the basic good of life can be overlooked because of other values achieved in that action. Their approach presumes some kind of calculus to compute when other values outweigh the good of human life. It also assumes that acts like mercy killing are not irreversibly evil in themselves. But indeed, such acts are always evil because they are opposed to the intrinsic good of human life.

The positions of Fletcher *et al.*[9] must be rejected because underlying their philosophy is consequentialism and this dualistic view that human life is only an instrumental good. Every kind of consequentialism involves a common feature: they all require the weighing of values or goods implicit in various alternatives. It is precisely because of this feature that it is an unworkable theory of moral reasoning.

It is not that consequentialism gives wrong answers, but that it cannot rationally justify any moral judgement, because it is an altogether unworkable way to proceed from an appreciation of the basic human goods to judgements on the moral quality of human acts. It is hard to see how any basic good would be rationally weighed against another. How, for example, is the life of a severely defective infant to be weighed against the costs of treatment, the burdens to the child's parents and society, and so on?

That life and other basic human goods are incommensurable is implied by the fact that human individuals can make free choices. One can make a free choice only between options which embody incommensurable goods. If possibilities which initially seemed to offer significant alternatives turned out not to embody any incommensurable goods, then one's judgement would be determined and no choice would be necessary. Other possibilities would simply fall away in favour of the one which appeared best. If goods were commensurable then there would be no need for free choice, since in each case of deliberation one could discover by calculation which alternative was the best.

Consequentialists like Fletcher must either accept the unworkability of their theory because of the incommensurability of goods, or admit the pointlessness of moral reflection because of a lack of free choice.

However, although consequentialism is wholly unworkable as an ethical theory, it is quite serviceable both as a method of rationalization and as a form of persuasive discourse by which one can formulate one's personal preferences and prejudices in a language of "goods".

Under this analysis, abortion is no different from euthanasia and is immoral for exactly the same reason. It too is killing in the strict sense. Yet it will be objected that some who carry out euthanasia or abortion are motivated by genuine sympathy for others. I do not deny this, though I suspect that the movement for euthanasia, and certainly for abortion, is motivated by a desire to get rid of the burden of unwanted people.

But the important point is that sympathy, like patriotism, racism, and sexism, can lead to grossly immoral acts. These emotions are morally neutral in themselves. They do permit one, however, to act immorally while seeming not to act out of self-interest. Sympathy, together with a fanatical attachment to the good of avoiding pain and suffering, can lead to grossly immoral violations of the good of life and the rights of others in the killing of people for reasons of mercy. Ultimately, practical reason both prohibits the killing of persons and obliges us to provide loving care for them.

## *REFERENCES*


1. Grisez G., Shaw R. Beyond the New Morality. University of Notre Dame Press, London,1980.
2. Beneficent Euthanasia. Marvin Kohl, ed., Prometheus Books, Buffalo, 1975
3. Fletcher J, Moral Responsibility: Situation Ethics at Work. Philadelphia: Westminster Press, 1967
4. Religious persons might be concerned that a firm rejection of dualism will undercut the belief in life after death. It is important, however, that for many Jews and for the common Christian tradition, the key to personal existence beyond the present life is in the resurrection of the body. This would make little sense of the person were not, in fact, a bodily being.
5. Maritain J. The Person and the Common Good, Chapter III: Individuality and Personality. See also Mounier E. Personalism, Part One, Chapter I: Embodied Existence.
6. Sullivan T. Active and Passive Euthanasia: An Impertinent Distinction? In T Mappes and J Zembaty, eds. Biomedical Ethics. McGraw-Hill, New York, 1986.
7. Ramsey P. The Patient as Person. Yale University Press, New Haven, Connecticut,1970.
8. Ramsey P. Ethics at the Edges of Life. Yale University Press, New Haven, Connecticut,1978.
9. Finnis J., Fundamentals of Ethics. University Press, Washington D.C., 1983.


### *Essays In Biomedical Ethics*

Prizes totalling $500.00 will be available for the best essay(s) on biomedical ethics submitted by undergraduate medical students. The topics may include clinical ethics, issues in physician education, personal ethical experience involving patients or health care professionals, issues of health policy and resource allocation or others. The essay should address the following questions: Is there a stated point to the essay? Is the point important? And, is the point addressed in an organized manner and supported by critical argument?

Dr. Eric Meslin, Biomedical Ethicist, 480-4818, and Dr. Neil Lazar, Physician, 340-3438, will be available to provide advice on topics and reference materials. Essays should be submitted to Dr. John Senn, Clinical Ethics Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Ave., Toronto, M4N 3M5 by March 15, 1991. Provided the essays are of sufficient quality, decision as to the winning submission will be made by May 30, 1991. The winning essay(s) will be published in the University of Toronto Medical Journal.

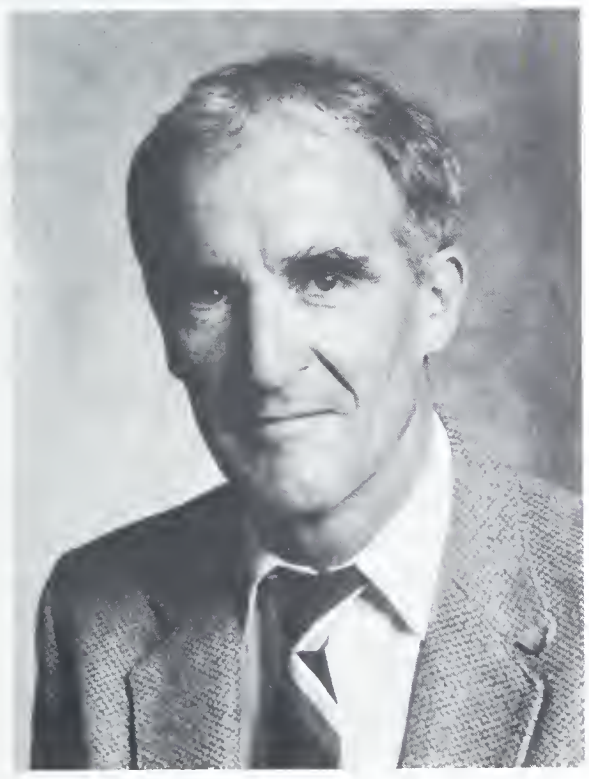
# The 1990 Gairdner Foundation International Awards

*Paul Ellis, M.Sc., 9T2*

Seven scientists from England, The United States and Canada were each recipients of the 1990 Gairdner Foundation International Award. The winners were selected by the Foundation's Medical Advisory Board that is chaired by Dr. Charles Hollenberg, President of the Foundation. The awards were presented to each scientist on Friday, November 2, 1990 by Professor J. Robert Prichard, President of the University of Toronto. Since it's establishment in 1957, the Foundation has honoured 212 scientists, 36 of whom have subsequently received the Nobel Prize.

Each winner received $ 30,000 Canadian to help further their research. Dr. Francis Collins, from the University of Michigan Medical Center, Ann Arbor, Michigan, USA, and Drs. John R. Riordan and Lap-Chee Tsui, from the Hospital for Sick Children, Toronto, Canada were recognized for their contributions to the identification and analysis of the cystic fibrosis gene. Dr. Victor Ling from the Ontario Cancer Institute, Toronto, Ontario, Canada was honoured for his discovery of one of the ways cancer cells can resist chemotherapeutic agents. For their discovery, development and application of methods that allow the separation and identification of proteins and nucleic acids, Dr. Oliver Smithies, University of North Carolina at Chapel Hill, N. Carolina, USA and Dr. Edwin M. Southern, University of Oxford, England, received the 1990 Gairdner Foundation International Award. Development of bone marrow transplantation as a therapy for leukemia and other life-threatening blood disorders earned Dr. Donnall Thomas, from the Fred Hutchinson's Cancer Research Center, Seattle, Washington, USA the 1990 Gairdner Foundation International Award.

*Dr. Lap-Chui Tsui*



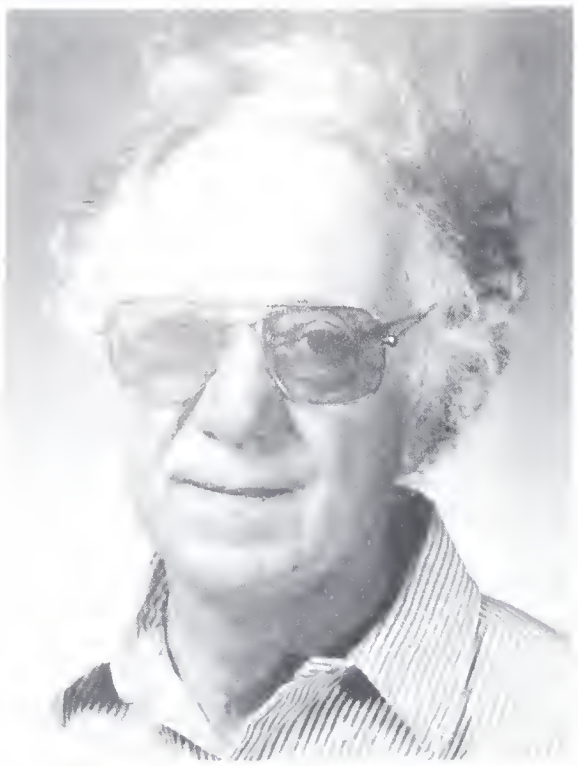
*Dr. John R. Riorden*

The Gairdner Foundation International Awards were first established in 1957 by the late James A. Gairdner. He was born in Toronto, Ontario, Canada in 1893. A lieutenant in the Canadian Army during World War I, he retired in 1918 with a rank of Major. He always showed an interest in clinical medicine and medical research and believed that the achievements of medical scientists should be recognized. After eight years of living with arthritis and with encouragement of Wallace Graham, a leading rheumatologist in Toronto, he established the Gairdner Foundation International Awards. The awards were initially given to medical scientists in the fields of arthritis, rheumatism and heart disease. Today the awardees come from many different areas of medical research.

## *Identifying the Cystic Fibrosis Gene*

The total human genome consists of 3 billion base pairs and the gene for cystic fibrosis (CF) forms less than 1/10,000th of this. Dr. Collins made the analogy that locating the CF gene was like looking for someone in a park and the only guide to their whereabouts was that they were located somewhere in our galaxy. Dr. Collins with the help of Lap-Chee Tsui and John R. Riordan, were the first to clone the human gene by closing in on its location on the human chromosome, without prior knowledge of the protein that produces and without the help of chromosomal rearrangements that might give an hint of its position. Dr. Collins, Tsui and Riorden and their colleagues accomplished just this feat and this was announced in 1989.

*Dr. Francis Collins*



*Dr. Oliver Smithies*

The story began five years earlier when Dr. Tsui and colleagues localized the CF gene to the long arm of chromosome 7. The researchers then located two markers flanking the CF gene. The Cf gene was now narrowed down to a segment of only one million base pairs. Dr. Tsui started walking along the chromosome to locate the gene responsible for CF. The process was speeded up by a technique, developed by Dr. Collins, called chromosome hopping. When the gene was located the structure of the corresponding protein was deduced by Dr. Riordan and his group. It was a transmembrane protein and was given the name CF transmembrane regulator (CFTR).

Sequencing of the CF gene has led to the finding that CF mutations are due to a loss of three base pairs coding for one amino acid in the CFTR protein. This knowledge along with other mutations in CFTR that cause CF can be used to develop accurate screening test for carriers and prenatal diagnosis for those at risk.

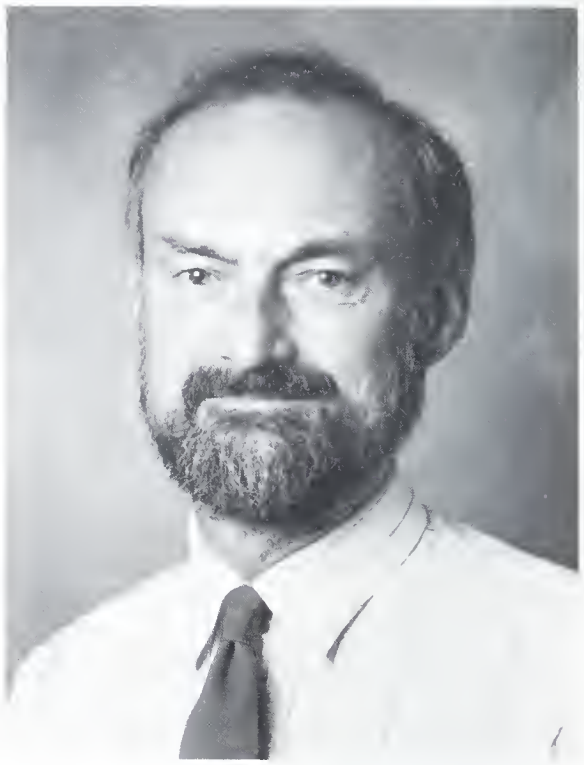
CF affects one child in 2000 births in people of European descent and one person in 20 is a carrier. CF is a recessive genetic disease that affects the lungs and pancreas. Although the symptoms can be ameliorated by treatment, there is no cure. Knowledge of the normal protein and changes within it that may be responsible for the diverse symptoms of CF may allow the development of therapy to correct the defect rather than just treating the symptoms. Dr. Collins, Tsui and Riordan using the tools of molecular genetics have brought us one step closer to realizing our goals for a cure for CF.

## *Separation and Identification of Substance for Life*

Much of what we accomplish in any research endeavor is dependent on those who have studied the problems before us. Often our understanding of a problem is limited because we lack the techniques to answer our questions. The ideas for the new techniques are usually generated from our past experiences and in retrospect are so beautiful in their simplicity. Nothing could be more true than the techniques developed by Drs. Smithies and Southern for the separation and identification of proteins and nucleic acids. Without them, we would have not been able to do DNA fingerprinting or isolate the genes for Duchenne Muscular Dystrophy and CF, just to name a few.

Dr. Oliver Smithies, while working at the Hospital for Sick Children in Toronto, was looking for an alternate way to separate serum proteins. The standard technique at the time was electrophoresis of serum proteins on cellulose acetate strips. The resolution of the proteins was poor at best. Trying to think of other mediums to separate the proteins in, Dr. Smithies remembered that starch, after his mother had finished doing the laundry, would solidify into a gel. Using a starch gel in place of the cellulose acetate strips gave a better resolution during the separation of the serum proteins.

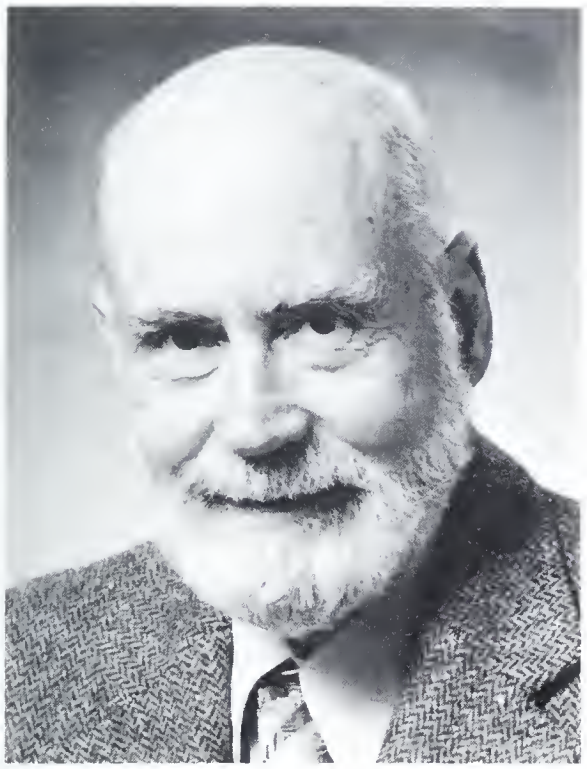
*Dr. Victor Ling*



*Dr. Edwin M. Southern*

Dr. Southern devised a technique which bears his name. The Southern blot method of DNA analysis was spawned from a childhood experience. Dr. Southern was an exceptional student who helped the teacher make multiple copies of examination papers. Not having photocopiers back then, the questions were written on a block that was impregnated with ink. Copies were made by over-laying the block with paper to which the questions were immediately transferred. The Southern blot technique is almost this simple. DNA is isolated and then fragmented with the use of endonucleases. The DNA fragments are separated by size in a gel matrix under the influence of electric field. The DNA fragments are then transferred or blotted onto filter paper. Their presence is then detected by the use of specific radioactive tag. Southern blots have spawned a serious of spin off techniques for RNA (Northern blot), protein (Western blot) and combinations of protein, DNA and RNA (Southwestern and Northwestern blots).

Modern day biochemistry would not have progressed as far or as fast as it has without the ingenuity of Drs. Smithies and Southern.



*Dr. Donnall Thomas*

# Drug Resistance in Cancer Cells

***JoAnn Majerovich, 9T2***

Chemotherapeutic agents are a vital component of cancer treatment. Clinically, they are used to treat cancer with the intention of cure or for palliation. They are used alone or in combination with other chemotherapeutic agents of other treatment modalities to improve therapeutic effectiveness. However, the major drawback of chemotherapy has been the spontaneous resistance of cancer cells to chemotherapeutic agents (multidrug-resistance). It is therefore crucial to understand the mechanisms of drug resistance to chemotherapeutic agents.

Dr. Victor Ling has discovered a mechanism which may account for this phenomenon. He and his associates have identified a molecule, P-glycoprotein, which is present on the cancer cells of many patients who are not responding to treatment. The amount of P-glycoprotein expressed on the cell membrane correlates with the degree of resistance. The expression of P-glycoprotein is associated with increased efflux of drugs in the multidrug resistant cells. Drugs have been proposed to bind directly to P-glycoprotein and then be actively pumped from the cell through a channel formed by many transmembrane domains of P-glycoprotein.

P-glycoprotein may play a crucial role in determining the clinical response of cancer patients to chemotherapy. It may be possible to follow tumour progression with P-glycoprotein. The efficacy of chemotherapeutic agents may be improved by targeting drugs or antibodies to P-glycoprotein to sensitize resistant tumour cells.

# Marrow Miracleworker

***Lily Angelov, 9T2***

Most of us clearly recall the national and later international media campaign in the spring and summer of 1990 for volunteers who might have HLA matched blood and marrow with the young Oriental girl in Toronto who had aplastic anemia. In her case as well as for many other patients with hematological disorders, the only hope for significant survival is a bone marrow transplant. Conceptually this therapeutic modality has been considered for several decades now, but its clinical application has been fraught with many biological and medical obstacles. The pioneering work in human bone marrow transplant procedures was begun in the 1950's by Dr. E. Donnall Thomas and he eventually headed the world's largest transplant program in Seattle for more than 15 years. In 1990 he was recognized for his outstanding contributions by receiving both a Gairdner Award and a Nobel Prize for Medicine. Dr. Thomas's early work involved the study of transplantation in several animal models where a substantial extent of immunobiology came to light and complemented the then burgeoning field of immunology. In 1956, Dr. Thomas's group was the first to demonstrate that donor bone marrow could be safely infused in humans with, in some cases, transient marrow engraftment. The applicability of such a technique in the treatment of a wide variety of immunological, hematological, and malignant diseases was easily appreciated and led to further experiments in this area. However, after this initial startling advance, the following decade of research showed bone marrow transplantation to be a highly complex procedure from the biological point of view and was laden with rather unanticipated setbacks. Among the first patients to be transplanted were those with aplastic anemia who had a monozygotic twin, a syngeneic transplant. In this type of transplant there is no immunological barrier to engraftment. The successful marrow recovery in these cases was encouraging with long term survival of these patients. However, this same approach of syngeneic transplantation was not as straightforward when used in patients with hematologic malignancy because of the additional requirement of first eliminating the disease. In this setting the malignant marrow of these patients was ablated by the use of lethal irradiation (+/- chemotherapy), followed by infusion of normal marrow from the identical twin. While here too, as with the aplastics, engraftment resulting in normal hemopoiesis was successful, the actual eradication of the leukemia was difficult. The appropriate radiation dose as well as the dose and type of chemotherapy had to be determined. This was achieved, yet most patients still relapsed within a few months of their transplant. With the advances in histocompatibility typing in the 1970's, leukemic patients could now be transplanted with marrow from non twin siblings who were an HLA match (25% probability of a match), a so called allogeneic transplant. This opened the door for many more patients to undergo transplantation. In these patients marrow engraftment occurred in most instances. Furthermore, as compared to the syngeneics, there was a lower relapse rate, raising the question of an immune surveillance mechanism in cancer that would have been inoperative in the syngeneic situation. How-

ever, an even worse problem manifest itself in these patients, an entity known as graft versus host disease (GVHD). GVHD is an immunological attack by donor lymphocytes on specific target organs, namely the skin, liver and G.I. tract, resulting in a high mortality in the first 100 days post transplant. In a paper written in 1975, Thomas and his colleagues proposed a now standard clinical classification system of GVHD, allowing for advances in prevention and treatment of GVHD to be systematically assessed. Although GVHD currently remains a significant clinical problem, Dr. Thomas and his colleagues have been responsible for many advances in its treatment. Unfortunately these treatments often result in severe immunosuppression associated with overwhelming infections. In attempting to address this complication, the Seattle group has developed many sucessful prophylactic and therapeutic measures. As a result of these efforts, up to 50% of leukemic patients are now cured with allogeneic transplantation. Nevertheless many obstacles remain - foremost is the lack of HLA identical sibling donors in most patients. Dr. Thomas and his Seattle group are again at the forefront of efforts to overcome this problem by using matched unrelated donors; their preliminary results are very encouraging. Despite the many problems which remain in the field of bone marrow transplantation, Dr. Thomas's achievements have made this a viable therapeutic approach for many diseases that were previously untreatable. Hence, it is on the shoulders of this remarkable man of medicine upon which we stand to look at a promising future in this field.

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# Ophthalmology in India

*Richard Hudson Johnston, 9T2*

A medical elective in India certainly offers a chance to experience a different culture and different approaches in medicine. The hospital I was at, Sankara Nethralaya, was inaugurated almost twelve years ago. The founder, Dr. Badrinath, opened this non-profit Ophthalmology hospital in Madras after extensive training in the United States. It offers excellent eye care in all areas of ophthalmology, specializing in vitreo-retinal problems making it a leader in this field in India. The facilities in the hospital including the medical equipments are comparable to those in North America. People are referred from all over India, Nepal and other nearby countries to receive treatment from this institution. Dr. Badrinath has also initiated a training programme in vitreo-retinal care that has vastly expanded the number of specialists in this field in India. After twelve years of work, Dr. Badrinath can say that he has masters in this field doing excellent work all over the country. The institute is certainly dedicated to teaching. Its staff trains ophthalmology residents, optometry students, and is initiating a nursing programme this fall. It is an academic center that has an atmosphere which stimulates people to learn. All the staff doctors continue to read about, and incorporate all new ideas in the field of Ophthalmology. The staff work very long, demanding hours and are truly dedicated to their profession. It was a great opportunity to be a part of this instituition over the summer.

*Dr. Ravi Sankar administering laser treatment to a patient at Sankara Nethralaya, Madras India.*

When I arrived in Madras I met Dr. T S. Surrendran who was my project coordinator. The drive into Madras was my first of many cultural shocks. I thought for sure that I would not make it to Sankara Nethralaya without an accident. We dodged pedestrians, cows, carts, scooters, rickshaws, autorickshaws, and oncoming traffic.

The daily routine for me at the hospital started at 8:00 and finished at 5:00, Monday to Saturday. Every second Sunday the hospital ran an "eye camp" that treated all patients free of charge thereby making the hospital accessible to all people regardless of there ability to pay. There were also six hours of lectures per week that were attended by both students and consultants (staff doctors). Each class had a resident or consultant presenting a topic and a consultant who would critique the talk at the end and chair the discussion that would follow. Topics would cover a wide range of areas such as corneal ulcers, diabetic retinopathy, and glaucoma.

Dr. Surrendran posted me with different doctors that would focus primarily, but not exclusively, on a particular area of Ophthalmology. The areas I spent the most time on were anterior segment problems (eg. corneal ulcers, glaucoma), posterior pole (mainly diabetic retinopathy), and refraction. The consultants would first point out normal features and show me how to use some of the specialized instruments. Some instruments that I had experience with were the slit lamp, tonometer, retinoscope, direct and indirect ophthalmoscopes. I learned the technique for each and improved considerably as time went on. Some instruments like the indirect ophthalmoscope were very difficult to use while others like the tonometer were simpler. As I gained more skills with the diagnostic instruments, the consultants would point out interesting pathologic findings to me such as corneal ulcers, anterior or posterior synechiae, etc.

I spent some time observing the doctors in the laser department. The three uses of the laser that I saw were for diabetic retinopathy, glaucoma, and for posterior capsulotomies. Most of the patients that I saw were being given pan-retinal photocoagulation for their diabetic retinopathy. During this procedure I examined the retina before and after laser treatment with the indirect ophthalmoscope as well as during the treatment with the teaching head of the laser.

I also spent some time in the outpatient department with some of the residents. This was the place where the initial history and examination was carried out. Here I saw many eye problems that were presenting in a late stage, often in a young patient. Many times there were people coming in with only one good eye, and one would learn that the other eye had gone blind due to a disease that could have been treated. It was a depressing thought and difficult to stomach. It was however gratifying to know that the patients good eye was being well cared for so the same fate hopefully would be avoided in this eye.

*Makeshift operating theatre at the Hosur Eye Camp, Tamil Nadu India.*

*Makeshift recovery room at the Hosur Eye Camp, Tamil Nadu India.*

During the last stage of my medical experience, I worked on a clinical project. The project was a concise, scientific, clinical trial designed to answer a significant question. The deeply pigmented eyes of the Indian people are difficult to dilate for fundus examination. They require multiple administrations of a dilating agent and it takes about an hour. Currently, the patients are instructed to keep their eyes closed throughout the entire one hour procedure. Having the eyes open would be more convenient for the patient and allow him/her to be more mobile and relieve some boredom. My project was designed to compare the effects of dilatation for fundus examination between two different clinical groups. The results showed no difference between the two procedures.

The project gave me the chance to really learn the concepts of a clinical trial. It really reinforced the ideas about scientific investigation, and gave me insight into the practical difficulties of running a clinical trial. It was my first introduction into the world of clinical medical research and was truly an invaluable experience.

To summarize, this summer elective gave me the chance to broaden my exposure in medicine. I learned some important fundamentals in both the clinical and research fields of Ophthalmology at one of the finest Ophthalmic teaching institutions in India. I was immersed in a culture that previously was so completely foreign to me. I learned to adapt to a new setting, to keep my mind open to new ideas, and to enjoy every new experience. For these opportunities, I am sincerely grateful to both Dr. S. S. Badrinath for his gracious hospitality, kindness, and guidance, and to the Medical Alumni Association of the University of Toronto for making this project possible.

# Lookout Within Our Borders

*Jean Chamberlain, 9T1*

'Go north you doctor, go north'. This has been the cry of the provincial government for ages and yet despite incentives and alluring packages young physicians remain 'in the south'. This has led to a chronic shortage of medical personnel in Northern Ontario. This trend may soon be reversed. Thanks to programmes such as the Sioux Lookout Programme which is geared to expose medical students, interns and physiotherapy students to the prospects of practice in the north.

Sioux Lookout is a town of 3,500 people which is located 250 miles north of Thunder Bay. The Sioux Lookout Zone covers an area of 285,000 km (roughly the size of France) in Northwestern Ontario. The population of the Zone is approximately 10,000 people. The native community of Sioux Lookout and the twenty native reserves within the zone are served by the Sioux Lookout Zone Hospital. The hospital itself is a 50 bed unit with a busy obstetrical ward.

During the month of June, 1990, I had the opportunity of visiting the Sioux Lookout Zone Hospital under the Sioux Lookout Programme sponsored by the University of Toronto. This month was part of my medical elective experience. The medical students and interns are funded for transportation costs to Sioux Lookout. Self-contained apartments situated across from the hospital are available for lodging.

The Zone is comprised of 27 native communities of which a 11 have nursing stations. The nursing stations are staffed by several nurses and serve smaller communities where no nursing stations are found. The nurses are trained to handle most patients who present to the station. Serious cases, however, can be airlifted to the Zone Hospital in Sioux Lookout. Most of these communities can be reached only by air.

The patient population at the Zone Hospital is composed primarily of native Indians of the Ojibway and Cree tribes. The ages range from neonate to the elders of the community.

During my elective at Sioux Lookout, I had many opportunities to make new acquaintances and enjoy the many facilities of the region. Social gatherings were frequent at staff member's cottages/homes and there were no shortage of opportunities to take advantage of the great outdoors. The beach was within walking distance and horse back riding stable open to the public was less than a mile away.

I was impressed by the quality of the medical equipment at the Zone Hospital. Brand new X-ray and ultrasound machines were recently purchased and the laboratory facilities were quite adequate. Any laboratory test which could not be completed at the Zone Hospital was sent to nearby facilities where it could be carried out. The staff in each of these departments were very helpful and I enjoyed one-on-one teaching and demonstrations of these important diagnostic tools.

My typical day began with rounds in the morning. Seven o' clock rounds with the haematology was a great way to get venipuncture experience. Some of the other rounds were grand teaching rounds, telemedicine rounds (linked to the Hospital for Sick Children) and general medicine rounds.

If I was scheduled to be on call for the day, I would then proceed to the emergency department where I would see 'walk-in' patients from the community with varying complaints. Throughout the morning, the satellite nurses from the reserves would contact the physician on call to discuss difficult patient cases which had been presented to the nursing station that day. A connecting telephone allowed the students to hear the conversation and be informed about the patient. As a result of one of these conversations, I participated in the airlifting of a child with bronchiolitis from the Cat Lake reserve.

In non-emergency cases, I would see the patient initially and complete a history and physical examination. In the situation of acute distress, I was able to accompany and assist the staff physician as he/she initiated the medical treatment. Translators were often necessary in communicating with elderly patients. It did not take long to learn to keep one's question short and to the point when using a translator!

Most pregnant women are flown to the Zone Hospital at 38 weeks of gestation. The women stay at the hospital's hostel. They need to attend the prenatal clinic weekly. Their food, lodging and transportation is financed by the federal government. One should not delay in taking a prolonged history from a native lady who feels like 'pushing'. Many of these women have had six or seven children and tend to deliver their babies rapidly. At my first delivery at the Zone Hospital, my patient had her baby within three minutes after entering the delivery room.

The patient volume tended to decrease in the evenings and contrary to the popular belief there were not a lot of midnight fight injuries. The next day would be filled by following the progress of patients admitted the day before. Outpatient clinics were usually held in the afternoon. Clinicians would closely follow our work and review pertinent findings in each case. Specialty clinics (orthopaedics, paediatrics and general surgery) would occasionally replace the general clinics and will be run by visiting consultants to the Zone Hospital. Radiologists also participate in locums at the Zone Hospital and not only review all the recent X-ray and ultrasound but offer teaching sessions for the medical staff of the hospital.

The operating room has a full schedule between the local surgeon's cases and those of the visiting surgical specialties. Students are free to participate in the O.R. as well. Paediatric dentistry is an important part of the native children care. Many suffer from bottle caries and their teeth are severely damaged by the age of three or four. General anaesthesia is required to treat many of their dental problems.

One of the highlights of my experience at the Sioux Lookout was the opportunity to accompany a physician on his visit to a nursing station in one of the native communities. I boarded a 10-seater 'Frontier' airplane with Dr. Egon, a consultant staff paediatrician from the Hospital for Sick Children heading for the Sandy River reserve. We were loaded with a supply of food and heavy military type sleeping bag in case of airplane difficulties.

The nursing station at Sandy River was recently constructed and contained a large clinic area and variety of facilities. The problems we encountered ranged from hearing impairment to failure-to-thrive and from sexual abuse to rare metabolic diseases. After the clinic, I was allowed to explore the community if I could avoid being exsanguinated by the black flies.

The Sioux Lookout programme was a definite asset to my medical education. Medically and culturally, it was a broadening experience and one that I would recommend to any fellow student. It has given me a new understanding of the native Canadians and their way of life and culture- an understanding that only comes with one-on-one interaction. The Sioux Lookout programme provides an opportunity to see and experience rural medicine like you will never see again.

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# Rapid Interpretation of Arterial Blood Gases and Pulmonary Function Test

*Elisabeth Van-Bussel, B.Sc., 9T2 and Anna Day, M.D., F.R.C.P. (C)**

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When evaluating a patient with a respiratory disorder it is important to be able to rapidly and correctly interpret the meaning of arterial blood gases and evaluate the pulmonary function. The types of information available include acid-base status, alveolar-arterial oxygen gradient and pulmonary function tests.

## Part I Acid-Base Analysis

**Acid-base balance:** A patient's acid-base balance can be divided into two main catagories based on blood pH, $paCO_2$ and $HCO_3^-$:

**Metabolic**

- **Acidosis**- Anion gap type or Non-anion gap type (table 1and table 2)
- **Alkalosis**- Chloride sensitive, chloride resistent or hybrid (table 3)

**Respiratory**

**Acidosis:**

**Acute** - e.g., drug overose, trauma

**Chronic** - e.g., COPD, cystic fibrosis

**Alkalosis:**

**Acute** - e.g., hyperventilation

**Chronic** - e.g., sepsis, pnemonia

**Table 1: Causes of Anion Type of Metabolic Acidosis**

| | Unmeasured anion | Disease |
|---|---|---|
| i. | Phosphate, sulphate | Renal failure |
| ii. | Ketone bodies | Diabetic ketoacidosis<br>Alcoholic ketoacidosis |
| iii. | Lactate | Hypoxia, Metabolic |
| iv. | Poison intake | |
| | Salicylate | Aspirin |
| | Formate | Methyl alcohol |
| v. | Assorted anion | |
| | Amino acid | TPN |
| | Acetate | High flux dialysis |
| | D-lactate | Bowel disease |

**Table 2: Causes of Non-Anion Gap Type of Metabolic Acidosis**

**i.** Ingestion of potential acids with chloride as the anion eg., hydrochloric acid, arginine or lysine hydrochloride. These are rarely seen or very obvious.

**ii. Bicarbonate loss:**

**a) Gastrointestinal:**

diarrhea, fistula, ileus, vomiting of bicarbonate rich fluids

**b) Renal:**

Failure of bicarbonate reabsorption: proximal renal tubular acidosis, carbonic anhydrase inhibitors.Failure of net acid excretion: distal tubular acidosis, defective ammoniagenesis

**iii.** Extracellular fluid volume reexpansion with sodium chloride

**iv.** Acidosis with increased blood anions which are inapparent because of: hypo-albuminemia, high blood levels of bromide or iodide or abnormal proteins which are cationic at pH 7.4.

**Table 3: Causes of Metabolic Alkalosis**

i. **Chloride responsive**: clinical features of intravascular volume contraction characterized by low urinary sodium chloride levels; will respond to chloride administration. eg., vomiting, gastric suction, diuretics, post-hypercapneic metabolic alkalosis.

ii. **Chloride resistent**: clinical features of intravascular volume expansion characterized by high urinary sodium chloride levels; will respond to treatment of underlying adrenal disorders. eg., primary hyperaldosteronism, adrenal hyperplasia.

iii. **Hybrid**: intravascular volumes and urine electrolytes are discordant. eg., heart failure, hypoalbunemia, milk-alkali syndrome etc.

The patient compensates for the acidemic and alkalemic state by adjusting the respiratory rate (to increase/decrease $pCO_2$) or by modifying $HCO_3^-$ production by the kidney. Such a compensation **does not** bring the pH back to normal range except in chronic respiratory alkalosis.

**Steps for determining the acid-base status**:

1. Determine whether the patient is **acidemic or alkalemic** (normal pH is 7.35-7.45)

   pH < 7.35 is acidemic

   pH > 7.45 is alkalemic

Even if the pH is within the normal range, it is important to continue the evaluation. The pH may be in the normal range for one of the three reasons: i) no acid-base disorder, ii) chronic respiratory alkalosis or iii) at least two acid base disorder.

2. Determine whether the disorder is **metabolic or respiratory**. If the pH and $paCO_2$ go in **opposite** directions then the disorder is **respiratory**. If the pH and $HCO_3^-$ go in the **same** direction, then the disorder is **metabolic**.
3. Determine if there has been **appropriate compensation**. Normal ratios of the changes in $paCO_2$ and $HCO_3^-$ seen in compensated acid-base disturbances are found in table 4. If there seems to be an 'inappropriate' compensation, then the presence of a second acid-base disorder must be considered.

**TABLE 4: RATIO OF $paCO_2$: $HCO_3^-$ IN SIMPLE ACID-BASE DISORDERS**

| | $paCO_2$* | $HCO_3^-$* |
|---|---|---|
| **Metabolic:** | | |
| acidosis | 1↓ | 1↓ |
| alkalosis # | 3↑ | 10↑ |
| **Respiratory:** | | |
| acidosis: | | |
| acute | 10↑ | 1↑ |
| chronic | 10↑ | 3↑ |
| alkalosis: | | |
| acute | 10↓ | 1↓ |
| chronic | 10↓ | 3↓ |

** Normal values $paCO_2$, 40 mm Hg; $HCO_3^-$, 24 mEq/L.*
*# will never rise above 50 mm Hg with compensation.*

4. Determine the anion gap for the cases of metabolic acidosis. Normal anion gap = [Na] – [(Cl) + ($HCO_3^-$)] = 10-15 mmol/L. Anion gap > 15 is anion gap-type of metabolic acidosis. Anion gap 10-15 is non-anion gap-type of metabolic acidosis.

## Part II Analysis of Oxygenation

Arterial oxygen tension: The aterial oxygen tension is normally in the range of 95-100 mm Hg. Generally, hypoxia is due to one of the following conditions: i) low inspired oxygen concentration, ii) hypoventilation and rise in alveolar $pCO_2$ and iii) increased alveolar-arterial oxygen gradient ($pAO_2 - paO_2$). Determining the arterial-alveolar oxygen gradient enables one to establish which of the above pathophysiologic conditions is responsible for low $paO_2$.

**Steps for determining causes of hypoxemia**

1. Determine the alveolar oxygen tension using the equation

$$pAO_2 = pIO_2 - pACO_2 \text{ where } pIO_2 = FIO_2 - (P_B - P_{H2O})$$

$$pACO_2 = paCO_2/R$$

$FIO_2$ = % oxygen in inspired air; $P_B$ = barometric pressure; $P_{H2O}$ = water vapour pressure; R = respiratory quotient (0.8)

2. Determine the arterial-alveolar oxygen gradient ($AaDO_2$)

$$(AaDO_2) = (pA0_2 - pa0_2)$$

Normal value is approximately 15.

3. Determine the cause of the hypoxemia as shown in figure 1.

**FIGURE 1: CAUSES OF HYPOXEMIA**

Hypoxemia ($paO_2$ < 95 mmHG)

- Increased A-a gradient (>15 mmHG)
  - interstitial lung disease
  - right to left shunting
  - V/Q mismatch
- Normal A-a gradient
  - $paCO_2$ elevated
    - hypoventilation
  - $paCO_2$ normal
    - low inspired $O_2$

## Part III Pulmonary Function Tests (PFT)

An assessment of a patient's pulmonary function may include the measurement of lung volumes, flow rates and diffusion capacity. These parameters can help to identify the extent of the patient's lung disease and any change in the patient's condition.

**Lung volumes:** Lung volumes can be measured using spirometry or flow-volume curves and gas dilution or body plethysmography (table 5).

**TABLE 5: LUNG VOLUMES**

| Parameter* | Definition |
|---|---|
| TLC | volume of lungs at full inspiration |
| RV | minimal end-expiratory volume |
| FRC | volume of lung at resting state |
| VC | volume difference between TLC and RV |
| RV/TLC | a ratio to indicate amount of air trapping |

**Total Lung Capacity (TLC), Residual volume (RV), Functional Residual Capacity (FRC), Vital Capacity (VC)*

**Flow rates:** Flow rates are measured using spirometry or flow-volume curves (table 6)

**Table 6: Flow Rates**

| Parameter* | Definition |
|---|---|
| FVC | Max. forced expiration from TLC to RV |
| $FEV_1$ | FEV in 1 second |
| $FEV_1/FVC$ | Airflow obstruction ratio (est.) |
| MMFR | Max Mid-expiratory Flow Rate |

** Functional Vital Capacity (FVC), Forced Expiratory Volume (FEV)*

**The diffusion capacity ($D_{CO}$):** $D_{CO}$ is the rate of diffusion of carbon monoxide from the alveolus to the capillary in relation to the partial pressure across the membranes. $D_{CO}$ is measured using inhalation techniques with carbon monoxide and helium.

$D_{CO}$ increases with: i) increased surface area, ii) increased hemoglobin and iii) increased pulmonary capillary blood volume. $D_{CO}$ decreases with: i) decreased surface area, ii) interstitial lung disease and iii) decreased hemoglobin.

Lung disease is classified into two main patterns of pulmonary function impairment: i) obstructive (obstruction to airflow) and ii) restrictive (decreased lung compliance). PFTs are very useful in delineating whether a patient has an obstructive or restrictive lung disease. Obstructive pattern is found in conditiond such as asthma, chronic bronchitis and emphysema. Restrictive pattern is found in interstitial lung diseases such as sarcoidosis, pulmonary fibrosis, hypersensitivity pneumonitis etc. Table 7 summarizes the changes in PFTs found in pulmonary disease.

**Table 7: PFT Showing Typical Restrictive and Obstructive Patterns**

| | Restrictive | Obsturctive |
|---|---|---|
| TLC (L) | ↓ | ↑ or N |
| FRC (L) | ↓ | ↑ or N |
| VC (L) | ↓ | ↓ or N |
| RV (L) | ↓ | ↑↑ |
| RV/TLC | N | ↑ |
| FVC (L) | ↓ | ↓ |
| $FEV_1$ | ↓ or N | ↓ |
| $FEV_1/FVC$ % | ↑ or N | ↓ |
| MMFR (L/s) | ↑ or N | ↓ |

**Steps to interpret PFT**

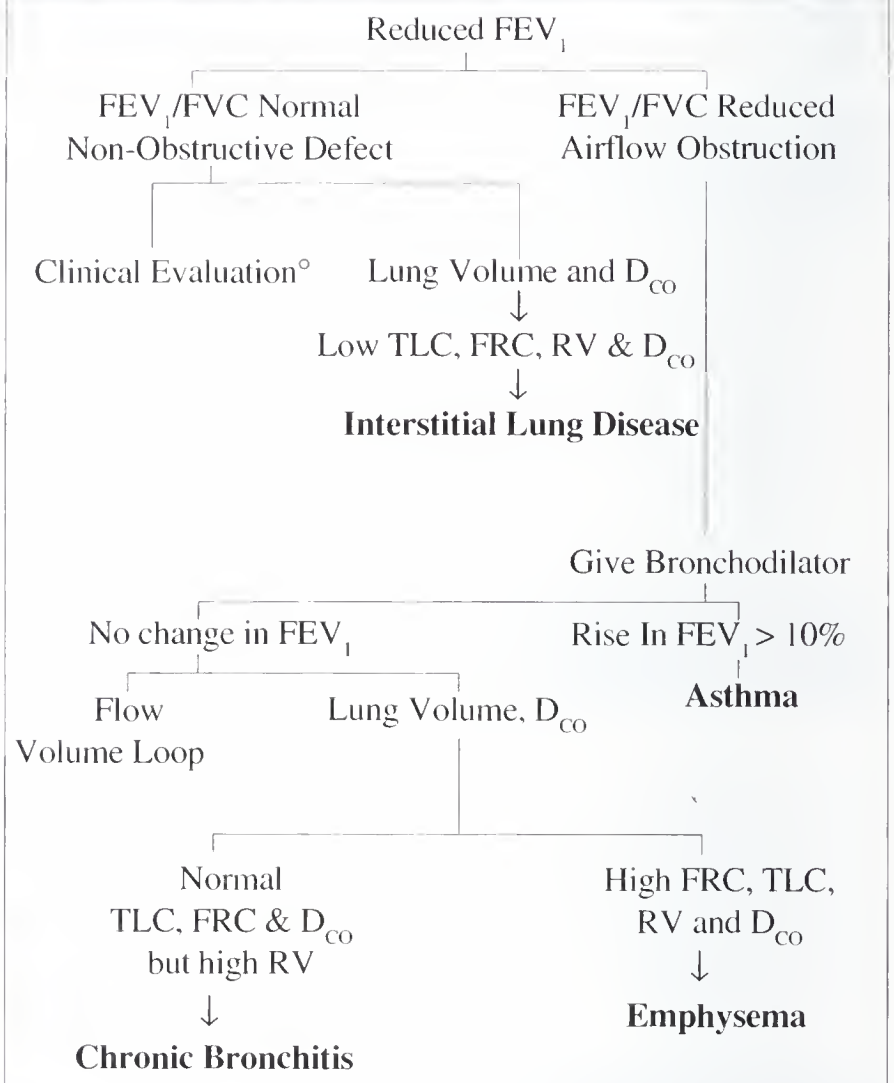
When interpreting PFT's predicted values are given on the basis of the patients sex, age and height. Normal PFT values are approximately 80% of the predicted values.

1. Follow figure 2 to characterize whether the disorder is obstructive or restrictive
2. If the general disorder is obstructive, then $D_{CO}$ will help to determine whether it is associated with tissue destruction of the alveoli (emphysema), vessels or if the lung parenchyma is preserved (asthma, chronic bronchitis).

$D_{CO}$↓ decreased = tissue destruction (eg., emphysema)

$D_{CO}$↑ increased or normal = tissue preserved (eg., asthma)

**Figure 2**
**Flow Chart for Assessment of Abnormal Spirometry***




° *Clinical Evaluation for Pleural effusion, Kyplio-scoliosis, Ankylosing spondylitis etc.*

* *Adapted from Allen, C.J. and Jones, N.L., Medicine, North America 22 April 1985.*

**Excercises**

A. Interpret the following arterial blood gases

| | pH | $paCO_2$ (mm Hg) | $HCO_3^-$ (mEq/L) |
|---|---|---|---|
| 1. | 7.33 | 54 | 29 |
| 2. | 7.31 | 29 | 13.5 |
| 3. | 7.21 | 70 | 27.3 |
| 4. | 7.56 | 48 | 46 |
| 5. | 7.45 | 25 | 17 |
| 6. | 7.58 | 25 | 22 |

**Answers:**

1. Primary chronic respiratory acidosis
2. Primary metabolic acidosis
3. Primary acute respiratory acidosis
4. Metabolic alkalosis
5. Chronic respiratory alkalosis
6. Acute respiratory alkalosis

B. Interpret the following PFTs

**Case 1:**

| | Predicted | Observed | % Predicted |
|---|---|---|---|
| TLC (L) | 6.1 | 8.2 | 134 |
| FRC (L) | 3.3 | 7.3 | 221 |
| VC (L) | 4.1 | 1.3 | 32 |
| RV (L) | 2.0 | 6.9 | 345 |
| RV/TLC | 32.7 | 84.2 | 257 |
| FVC (L) | 4.1 | 1.3 | 32 |
| $FEV_1$ | 3.1 | 0.4 | 13 |
| $FEV_1$/FVC % | 74.3 | 30.8 | 41 |
| MMFR (L/s) | 4.1 | 0.2 | 5 |
| $D_{CO}$ (ml/min/ mm Hg) | 22.7 | 3.8 | 17 |

Answer: This case demonstrates an obstructive pattern with severe gas trapping, airflow limitation and severe reduction in diffusion capacity.

**Case 2:**

| | Predicted | Observed | % Predicted |
|---|---|---|---|
| TLC (L) | 5.3 | 2.4 | 45 |
| FRC (L) | 3.3 | 1.5 | 45 |
| VC (L) | 3.2 | 1.1 | 34 |
| RV (L) | 2.1 | 1.3 | 62 |
| RV/TLC | 39.3 | 53.4 | 136 |
| FVC (L) | 3.2 | 1.1 | 34 |
| $FEV_1$ | 2.3 | 0.9 | 39 |
| $FEV_1$/FVC % | 72.4 | 81.8 | 113 |
| MMFR (L/s) | 3.2 | 1.6 | 50 |
| $D_{CO}$ (ml/min/ mm Hg) | 26.4 | 6.9 | 29 |

Answer: This case demonstrates severe lung restriction with proportionate reduction in vital capacity and $FEV_1$. The airway resistence is normal but there is severe reduction in diffusion capacity.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# Common Medical Diagnoses: An Algorithmic Approach.

*Healy, P.M. and Jacobson, E.J. W.B. Saunders Company, Toronto, Ontario, 1990; $48.25.(203 pages)*

Common Medical Diagnoses: An Algorithmic Approach is intended to provide a framework for the logical approach to the diagnosis of disease based on symptoms and laboratory findings. The book is designed such that for each major clinical finding there is an algorithm outlining the key laboratory investigations and the decision process leading to the correct diagnosis. The format is reminiscent of that found in Fluid, Electrolyte and Acid-Base Emergencies by Halperin and Goldstein which many U of T medical students will be familiar with.

The 200 page book is divided into 11 chapters, using a systems approach. Each chapter is divided into commonly encountered signs and symptoms or abnormal laboratory findings. Accompanying each algorithm is a very brief list (10 to 20) of clinical pearls relating to the topic of interest. In addition, each topic is cross-referenced to Wyngarden & Smith: Cecil Textbook of Medicine, 18th Edition, and Harrison's Principals of Internal Medicine, 11th Edition (**not** the new 12th edition). The table of contents is clear and concise, and the index at the back of the book is extensive, making this book quite easy to use.

The algorithmic approach to medical diagnosis of course presumes a relatively high level of familiarity with the subject material. This book will not make you a brilliant diagnostician if you don't already know your material. What it is intended to do is help you rapidly break down large bulky lists into smaller, more easily managed groups of diagnostic probabilities. To this end, Common Medical Diagnosis: An algorithmic Approach may prove useful to the medical student or house officer who lacks the experience to quickly get to the heart of the matter.

My personal opinion of the book is that I think I would be unlikely to carry it around with me in the hospital (it is not a pocket size book, no doubt due to the limits of legibility of the full page size algorithms), and therefore I think it would be of limited use as a practical tool. Having said that however, I must say that I think this book is a great way to quickly review a huge amount of material. Although concise, the pages of clinical pearls contain a lot of information. It is not difficult to find things in either Harrison's or Cecil's textbooks of medicine, but the cross-referencing to these books is kind of an added bonus.

In conclusion, I liked this book, and I think it will come in handy for reviewing material in general and before exams. The algorithms are similar to the ones we all construct for ourselves when studying for mid-terms and finals. In that sense they may be either useful to you, or deny you the exercise of thinking things through for yourself. If you are the kind of person who throws all your notes out at the end of the year, this may be just the review book for you. The relatively high price tag will probably prevent Common Medical Diagnoses: An Algorithmic Approach from being widely accepted.

*Bjug Borgundvaag, Ph. D., 9T2*

# Goodman and Gilman's "The pharmacological basis of Therapeutics".

*8th edition. A. Goodman Gilman, T.W. Rall, A.S. Nies and P. Taylor (Eds). 1811 pages, Pergamon Press (Collier Macmillan Canada Inc.). 1990. $95.00*

The first edition of this text was published in 1940. At that time, Louis Goodman and Alfred Gilman had three objectives in mind. They wanted their text to correlate pharmacology with the related medical sciences, to interpret the actions and uses of drugs from the viewpoint of important advances in medicine, and to emphasize the application of pharmacodynamics to therapeutics. It is hard to conceive of today, a pharmacology text with no mention of antibiotics, cancer chemotherapy, psycotherapeutics and many other classes of effective, useful, life saving drugs which we now take for granted. From these humble beginnings has developed the clinical and basic science of pharmacology.

In the first seven editions of "The Pharmacological Basis of Therapeutics", all of these advances, and the rationale behind the science have been chronicled in concise, well organized detail. This tradition continues with the eighth edition which remains true to the original objectives of the text. The virtual explosion of molecular biological techniques as a tools for understanding intracellular signalling pathways, intercellular communication and the modulation of these processes has necessitated substantial revisions of the previous version of this text which was produced in 1985. It is through the use of these tools that we now, for the first time, begin to truly understand the biochemical nature of the interaction between cells and chemical messengers, be they a drug, neurotransmitter or hormone, and the response these agents effect. The various authors and editors have risen to the challenge of this difficult task. They have surveyed the progress in each field, evaluated the significance of each advance, and present the results in a well written, easily read text.

The information in this book is presented in 18 sections. Each of these is further broken down into several chapters. The first section covers the general principles of pharmacokinetics, pharmacodynamics and the principles of toxicology and therapeutics. This is the backbone of pharmacology, presented in 83 pages. The remaining sections of the book are presented using a systems approach. Each section discusses the normal physiology of cellular communication within a system, and then describes the pharmacological manipulation of that system for therapeutic effect. Completely new sections to the eighth edition include discussions of drugs affecting gastrointestinal function, immunosuppressive agents and dermatopharmacology. Other sections have been substantially re-organized reflecting new research findings.

The scope and breadth of the subjects to be covered in this volume is enormous. In spite of this, the text remains concise and very well organized. It should be emphasized that this text is not a substitute for catalogues such as the Compendium of Pharma-

ceuticals and Specialities or the Physicians Drug Handbook. Goodman and Gilman's is a comprehensive textbook. I often find myself needing a concise review of the physiology of some system or other. I very often find what I need to know in this text.

The question remains, "Who should buy this book?". As someone with an interest in pharmacology, I am obviously biased. Nevertheless, I think this volume will make a useful addition to any medical student's or practitioners reference library. While it is not a cheap book, I believe it to be a good value. I urge you to take a look at it the next time you are in the bookstore or at the library.

*Bjug Borgundvaag, Ph. D., 9T2*

## Surgery: A Complete Guide for Patients and Their Families.

*A. Gross, P. Gross and B. Langer (Eds). Harper and Collins, Toronto. 288 pp. 1989. $49.95.*

At one time or another, just about everyone has to undergo a surgical procedure. Whether it is something as small as having tubes put into ones ear to something as major as resection of a brain tumour, having surgery can be a very traumatic experience.

This book, written by the Department of Surgery at the University of Toronto, takes the patient through many common surgical procedures and explains them in words the patient can relate to and understand. In his introduction, Dr. Langer states "This book is intended to bridge the gap between the surgeon, who perceives surgery as an everyday event, and the patient-for whom it may be a life crisis". This book does just that.

Also included are chapters on the hospital experience where the author explains the hierarchy within a teaching hospital as well as a community hospital, surgical research where clinical trials and animal experimentation are discussed, and complications of surgery.

Each chapter covers the common procedures within that specialty and includes diagnosis, treatment (both surgical and non-surgical), and recent advances in that field. The methods by which the procedures are carried out are explained within the body of each chapter along with possible complications and an estimate of recovery time. The anatomy and procedures are beautifully illustrated by the Faculty and students of The Department of Art as Applied to Medicine at The University of Toronto.

Most of the topics include case histories which demonstrate the cases of a typical patient who may undergo these procedures. They often include many of the common questions asked by patients and perhaps some of the possible answers. Each case history takes the reader through the procedure, and explains when the patient needs to be seen in follow-up.

This book is an excellent resource book not only for patients and their families as the title suggests, but also for medical students, physicians and allied health care professionals whose patients may be undergoing these procedures.

*Mark Bradley Noss, 9T2.*


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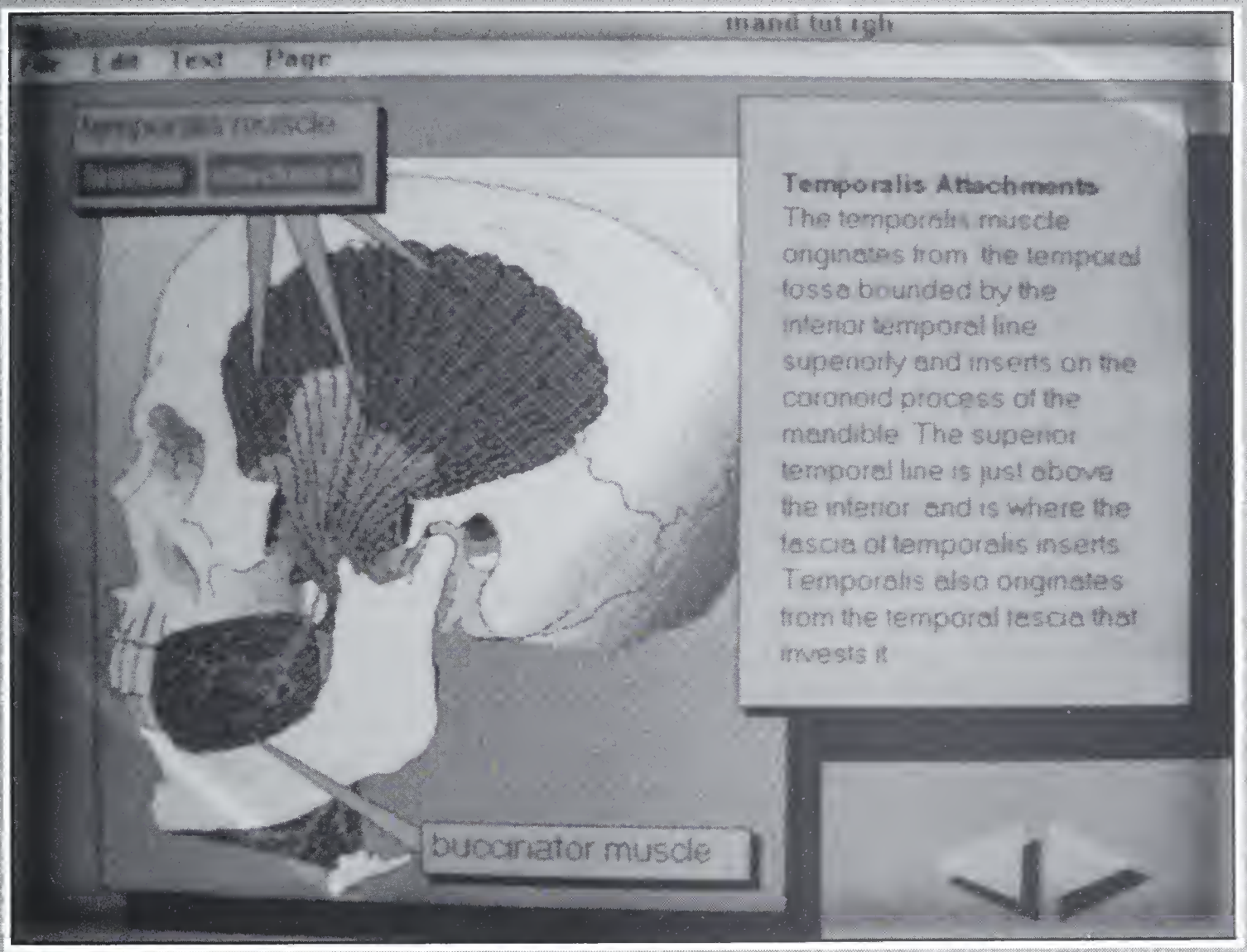
***Errata to Vol 68 No:1 1990***

1. *P.17 Table 2: 'Duration of initial dose' should read 'Duration of all doses'.*
2. *P.29 Figure 2: Illustration should show left knee straight.*
3. *P.30 Figure 3: Illustration should show left knee bent.*

# The Division of
# Biomedical Communications

Department of Surgery, Faculty of Medicine, University of Toronto, (formerly Dept. of Art as Applied to Medicine)


Temporalis Attachments
The temporalis muscle originates from the temporal fossa bounded by the inferior temporal line superiorly and inserts on the coronoid process of the mandible. The superior temporal line is just above the inferior and is where the fascia of temporalis inserts. Temporalis also originates from the temporal fascia that invests it
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***above**: from the computer assisted tutorial, The Mandibular Nerve, by Rick Kogucki, third year student.*

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